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Effects of Atomoxetine and Methylphenidate on functional brain activation in Medication-naïve children with Attention Deficit Hyperactivity Disorder

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Effects of Atomoxetine and Methylphenidate on functional brain activation in medication-naïve children with Attention Deficit Hyperactivity Disorder

Ana Isabel Cubillo Fernandez

**Thesis submitted to the University of London
for the degree of Doctor of Philosophy**

**Institute of Psychiatry, King's College London
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ABSTRACT

The present functional magnetic resonance imaging (fMRI) study compared the effects of two commonly prescribed medications for Attention Deficit Hyperactivity Disorder (ADHD), the stimulant methylphenidate (MPH), and the non-stimulant Atomoxetine (ATX) in ADHD.

Brain activation and task performance during motor inhibition (Stop), time discrimination (TD) and working memory (WM) tasks were compared in 20 medication-naïve ADHD boys (10-17 years-old) after a single dose of MPH (0.3mg/kg), ATX (1mg/kg) or placebo (Vit C, 50mg) using a randomized, double-blind, placebo-controlled design. To test for potential normalization effects, brain activation in patients under each drug was compared to that of 20 age-matched unmedicated healthy boys.

Both drugs showed task-dependent drug-specific and shared effects. Performance-wise, only MPH improved inhibitory speed and reduced TD errors in patients, while both drugs improved WM. MPH relative to ATX upregulated and normalised underactivation in patients relative to controls in right VLPFC and cerebellar/occipital areas during motor inhibition, in left IFC during TD and WM and in left putamen and SMA/ACC during TD. During WM, ATX showed drug-specific upregulation and normalisation effects relative to MPH in right DLPFC, which was reduced in patients relative to controls.

Shared effects were normalisation of underactivation in patients relative to controls in left VLPFC during motor inhibition and in right VLPFC during TD. During WM, both drugs enhanced performance-associated fronto-temporo-striatal activation and deactivated default-mode network regions in patients relative to controls.

In conclusion, ATX and MPH have task-dependent drug-specific effects on task-relevant prefrontal regions, suggesting different mechanisms of action despite their shared prefrontal catecholaminergic effects. Their differential prefrontal lateralisation suggests potentially stronger effects of MPH on left-lateralised dopaminergic networks, and of ATX on right-lateralised noradrenergic networks. Their shared effects were not restricted to prefrontal regions or task-positive networks, but extended to default-mode networks, suggesting they act on wider dopaminergic and noradrenergic neural networks.

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LIST OF ABBREVIATIONS USED THROUGHOUT THE THESIS

ADHD:	Attention Deficit Hyperactivity Disorder
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders, 4 th Edition, Text Revised
SDQ:	Strengths and Difficulties Questionnaire
SCQ:	Social Communication Questionnaire
CPRS:	Conners' Parent Rating Scale
EF:	Executive Functions
WM:	Working Memory
TD:	Time Discrimination
SST:	Stop Signal Task
GNG:	Go/NoGo Task
CPT:	Continuous Performance Test
SSRT:	Stop Signal Reaction Time
SSD:	Stop Signal Delay
MRT:	Mean Reaction Time
SD of RT:	Standard Deviation of Reaction Time
ISV:	Intra-Subject Variability
MPH:	Methylphenidate
ATX:	Atomoxetine
DA:	Dopamine
NE:	Norepinephrine
DAT:	Dopamine Transporter
NET:	Norepinephrine Transporter
LC:	Locus Coeruleus
SN:	Substantia Nigra
sMRI:	Structural Magnetic Resonance Imaging
fMRI:	Functional Magnetic Resonance Imaging
EEG:	Electroencephalography

DTI:	Diffusion Tensor Imaging
PET:	Positron Emission Tomography
SPECT:	Single Photon Emission Computed Tomography
BOLD:	Blood-Oxygen Level Dependent
IFC:	Inferior Prefrontal Cortex
OFC:	Orbitofrontal Cortex
DLPFC:	Dorsolateral Prefrontal Cortex
VLPFC:	Ventrolateral Prefrontal Cortex
VMPFC:	Ventromedial Prefrontal Cortex
MFC:	Medial Frontal Cortex
SFC:	Superior Frontal Cortex
PFC:	Prefrontal Cortex
ACC:	Anterior Cingulate Cortex
PCC:	Posterior Cingulate Cortex
VS:	Ventral Striatum
ITG:	Inferior Temporal Gyrus
MTG:	Medial Temporal Gyrus
STG:	Superior Temporal Gyrus
IPL:	Inferior Parietal Lobe
SPL:	Superior Parietal Lobe
DMN:	Default-Mode Network

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Ana Cubillo
May 2012

CHAPTER 1. NEUROPSYCHOLOGICAL EVIDENCE OF COGNITIVE DEFICITS IN ADHD

1.1 Introduction: Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, characterised by age-inappropriate symptoms of inattention and hyperactivity/impulsivity (American Psychiatric Association, 2000), and its prevalence is estimated to be between 3-8% in school-aged children (American Psychiatric Association, 2000; Froehlich et al., 2007; Merikangas et al., 2010). Although traditionally conceptualised as a childhood disorder, it is now accepted that it persists into adulthood in up to 65% of the cases (Barkley, Fischer, Smallish, & Fletcher, 2002; Biederman et al., 2006; Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Taylor, Chadwick, Heptinstall, & Danckaerts, 1996; Weiss, Hechtman, Milroy, & Perlman, 1985), affecting 4% of the adult population (Faraone & Biederman, 2005; Kessler et al., 2006).

The Diagnostic Statistical Manual of Mental Disorders (4th Edition, text revision) (American Psychiatric Association, 2000) is a descriptive symptom-based classification, as an attempt to avoid theory-based classifications which were predominant in previous versions of the DSM. According to this international classification, symptoms of ADHD are clustered into three different domains, including inattention (e.g. difficulties in sustaining attention during school/work, easily distracted by external/internal stimuli, careless mistakes in school/work, difficulties in following instructions, forgetful), hyperactivity (e.g. fidgety, always on the go) or impulsivity (e.g. intruding in conversations, difficulty to wait his/her turn, excessive talk) (Table 1.1.). ADHD is therefore characterised by the heterogeneity of the symptoms presented by the patients, addressed by the international classifications by grouping them in different subtypes depending on the number of symptoms present in each domain (inattentive, hyperactive, combined subtypes) (American Psychiatric Association, 2000).

Table 1.1. DSM-IV-TR Diagnostic criteria for ADHD

DSM-IV-TR DIAGNOSTIC CRITERIA FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER
<p>A. Either (1) or (2):</p> <p>1. INATTENTION: Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with the developmental level:</p> <ul style="list-style-type: none"> (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities (b) often has difficulty sustaining attention in tasks or play activities (c) often does not seem to listen when spoken to directly (d) often does not follow through on instruction and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behaviour or failure to understand instructions) (e) often has difficulty organising tasks and activities (f) often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books or tools) (h) is often easily distracted by extraneous stimuli (i) is often forgetful in daily activities <p>2. HYPERACTIVITY-IMPULSIVITY: Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:</p> <p>HYPERACTIVITY:</p> <ul style="list-style-type: none"> (a) often fidgets with hands or feet or squirms in seat (b) often leaves seat in classroom or in other situations in which remaining seated is expected (c) often runs about or climbs excessively in situations in which is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness) (d) often has difficulty playing or engaging in leisure activities quietly (e) is often "on the go" or often acts as if "driven by a motor" (f) often talks excessively <p>IMPULSIVITY:</p> <ul style="list-style-type: none"> (g) often blurts out answers before questions have been completed (h) often has difficulty awaiting turn (i) often interrupts or intrudes on others (e.g., butts into conversations or games) <p>B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years</p> <p>C. Some impairment from the symptoms is present in two or more settings (e.g. at school [or work] and at home)</p> <p>D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.</p> <p>E. The symptoms do not occur exclusively during the course of a <u>Pervasive Developmental Disorder</u>, <u>Schizophrenia</u>, or other Psychotic disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, dissociative Disorders, or a Personality Disorder).</p> <p><i>In making the diagnosis of ADHD, a child or teen is show symptoms that fit in one of three subtypes:</i></p> <p>314.01 Attention Deficit/Hyperactivity disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months.</p> <p>314.00 Attention Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months.</p> <p>314.01 Attention Deficit/Hyperactivity disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months.</p> <p>Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.</p>

ADHD is a very pervasive disorder, with high impact on academic and social development (Harpin, 2005), and high rates of psychiatric comorbidities both in

childhood (Biederman, Newcorn, & Sprich, 1991; Blackman, Ostrander, & Herman, 2005; Jensen, Martin, & Cantwell, 1997; Spencer, 2006) and adulthood (Kessler et al., 2006; McGough et al., 2005; Sobanski et al., 2007; Sobanski et al., 2008). Furthermore, the presence of psychiatric comorbidities in children with ADHD has been identified as a risk factor for the persistence of ADHD in adulthood (Biederman, Petty, Clarke, Lomedico, & Faraone, 2010; Lara et al., 2009).

Genome-wide, twin and adoption studies have shown high heritability of the disorder with some evidence for genetic associations, although no single gene has consistently been associated with ADHD and it is currently thought that ADHD may be associated with multiple genes of small effects (Faraone & Mick, 2010). The most consistent evidence so far suggests a role in the aetiology of ADHD for those genes coding for dopaminergic receptors DRD4 and DRD5, dopamine transporter (SCL6A3), serotonin receptor HTR1B and the aminoacid protein SNAP-25, part of a presynaptic plasma membrane protein involved in the regulation of neurotransmitters release (Faraone & Mick, 2010). However, not only genetic but also environmental factors need to be considered, as these may trigger, modify or exacerbate the presentation of the disorder (Thapar, Langley, Asherson, & Gill, 2007; Wermter et al., 2010).

1.2 Neuropsychological deficits in ADHD

Executive functions (EF) are high-level cognitive processes necessary for goal-directed behaviours (Stuss & Alexander, 2000). They include the abilities to form a goal, plan and carry out the goal-directed plan, as well as performance monitoring and modification of the plan according to the feedback in order to achieve the goal. Thus, EF involves planning, decision making, temporal foresight, working memory, higher level and selective attention, motor inhibition, interference control, set maintenance and set-shifting as well as integration across space and time (Stuss & Alexander, 2000).

EF can be differentiated between “cool” and “hot” (Zelazo & Muller, 2002). “Cool” EF are elicited by relatively abstract and de-contextualized problems and mediated by ventrolateral and dorsolateral fronto-striatal, fronto-cerebellar and fronto-parietal neural networks (Zelazo & Muller, 2002). On the other hand, “hot” EF involve affection and motivation, are elicited by paradigms loading on motivation and

reward, such as tasks of reward-related decision making, reversal of rewarded stimulus-response associations or temporal discounting and are mediated by mesolimbic ventromedial (VMPFC) and orbitofrontal (OFC)-striatal and limbic circuits (Zelazo & Muller, 2002).

Deficits in “cool” and “hot” EF have been observed in children with ADHD (for reviews, see Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Rubia, 2011). For example children with ADHD have deficits in motor inhibition (Alderson, Rapport, & Kofler, 2007; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Nigg, 2005; Oosterlaan, Logan, & Sergeant, 1998; Rommelse et al., 2008; Rubia, Oosterlaan, Sergeant, Brandeis, & von Leeuwen, 1998; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; Wodka et al., 2007), interference inhibition (Lansbergen, Kenemans, & van Engeland, 2007; Mullane, Corkum, Klein, & McLaughlin, 2008), switching (Gau & Shang, 2010a; Gualtieri & Johnson, 2006; Rhodes, Coghill, & Matthews, 2005; Willcutt et al., 2005), sustained attention (Huang-Pollock, Nigg, & Halperin, 2006; Willcutt et al., 2005) and working memory (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt et al., 2005).

Furthermore, there is evidence for deficits in reward-related decision-making tasks such as temporal discounting and gambling tasks (Garon, Moore, & Waschbusch, 2006; Luman, Oosterlaan, & Sergeant, 2005; Luman, Tripp, & Scheres, 2010; Toplak, Jain, & Tannock, 2005). ADHD is associated an enhanced preference for small immediate versus larger delayed rewards and to a decreased sensibility for reinforcement at a psychophysiological level (Luman et al., 2005; Luman et al., 2010), as well as with less advantageous choices during gambling tasks (Garon et al., 2006; Toplak et al., 2005).

Different theoretical models have tried to account for the cognitive deficits and symptoms observed in youth and adults with ADHD. Most of them hypothesise an etiological pathway linked to the cognitive dysfunctions observed, which would be related to the symptoms observed in the patients, and to the abnormal structure and/or function of the neural circuits underlying defective cognitive functions. Thus, behavioural inhibition processes were considered the “core” deficit, with underlying dysfunctions in fronto-striatal regions (Barkley, 1997). Sergeant (Sergeant, 2000) proposed an arousal/activation dysregulation, in which arousal deficits would be due

to a hypofunctioning right lateralized noradrenergic neural system (which would involve the mesencephalic reticular formation and amygdala), and activation deficits that would arise from a hypofunctional dopaminergic network (including basal ganglia/striatum). Deficits in working memory (WM) arising from a dysfunctional dorsolateral prefrontal cortex (DLPFC) have also been identified as core deficits for ADHD (Castellanos & Tannock, 2002). Sagvolden et al (Sagvolden, Johansen, Aase, & Russell, 2005) proposed an underfunctioning nigrostriatal dopaminergic branch that would lead to disrupted reinforcement processes. Finally, Sonuga-Barke (Sonuga-Barke, 2002) hypothesized a dual pathway model, with inhibitory deficits (mediated by the mesocortical branch of the dopaminergic system) and delay aversion (mediated by the mesolimbic dopaminergic branch associated with reward circuits) as the neural endophenotypes of ADHD.

However, these approaches have only been able to partially account for the deficits observed in patients with ADHD (Nigg, 2005). The available evidence shows that in any given cognitive deficit studied, there is always a proportion of children with ADHD that is not affected, whose performance overlaps with that of healthy control children (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010), which suggests that the cognitive aetiology of ADHD is more likely to be multifactorial. Recent attempts to explain this heterogeneity have suggested multiple developmental pathways for ADHD (Hart, Radua, Mataix-Cols, & Rubia, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2012; Makris, Biederman, Monuteaux, & Seidman, 2009; Nigg & Casey, 2005; Sonuga-Barke et al., 2010), with structural and functional abnormalities in shared but dissociable functional networks underlying the observed deficits (Makris et al., 2009; Nigg & Casey, 2005).

Furthermore, there is consistent evidence for deficits in other non-EF functions. For example, ADHD patients show consistent deficits in temporal processing (Rubia, Halari, Christakou, & Taylor, 2009; Toplak, Dockstader, & Tannock, 2006). In addition there is evidence for slower reaction time across tasks (Alderson et al., 2007; Gualtieri & Johnson, 2006; Klein et al., 2006; Lijffijt et al., 2005) and increased intra-subject variability (ISV) across a large range of cognitive tasks (Alderson et al., 2007; de Zeeuw et al., 2008; Epstein et al., 2003; Epstein, Langberg, et al., 2011; Klein et al., 2006; Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Oades & Christiansen, 2008; Rubia, Smith, Brammer, & Taylor, 2007a; Vaurio,

Simmonds, & Mostofsky, 2009). These differences in ISV have shown large effect sizes (Lijffijt et al., 2005), and high ability to discriminate between patients and controls (Rubia, Smith, et al., 2007a). Thus, ISV has been proposed as being potentially the most robust neuropsychological marker of ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). It has been suggested that increased ISV may be associated with difficulties in sustained attention, arousal or state regulation, thus involving noradrenergic transmission (Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003), to timing deficits with underlying cerebellar dysfunctions (Toplak, Rucklidge, Hetherington, John, & Tannock, 2003), and more recently to spontaneous low frequency activity in the Default Mode Network (DMN), which competes with task-related activation, leading to attention lapses and increased ISV (Sonuga-Barke & Castellanos, 2007).

Also, elongated mean reaction time (MRT) to stimuli has been reported consistently across different cognitive tasks (Alderson et al., 2007; Epstein, Langberg, et al., 2011; Gualtieri & Johnson, 2006; Kerns, McInerney, & Wilde, 2001; Klein et al., 2006; Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007).

In addition, children with ADHD have shown deficits in the context of reward (for reviews, see Luman et al., 2005; Luman et al., 2010). In line with the hypothesized disruption in reinforcement processes (Sagvolden et al., 2005), ADHD is associated with improved performance under reinforcement manipulations, with poorer performance under partial compared to continued rewards and with impaired reinforcement-learning and acquisition of behaviour (Luman et al., 2005; Luman et al., 2010). Reinforcement manipulations during time reproduction tasks have shown some effect on performance however, the deficits were improved but not remediated by motivational manipulations (Luman, Oosterlaan, & Sergeant, 2008; McInerney & Kerns, 2003; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005).

Thus, the most consistent neuropsychological deficits observed in children with ADHD are in tasks of motor response inhibition, sustained attention, temporal processing and working memory (for reviews, see Cubillo et al., 2012; Rubia, 2011), which are therefore the domains which were chosen for the fMRI tasks of this PhD. The evidence for neuropsychological impairment in these tasks will be reviewed below.

1.2.1. Deficits in inhibitory functions

1.2.1.1 Motor response inhibition deficits

Behavioural inhibition has traditionally been divided into three types of inhibitory processes: stopping of an ongoing response, inhibition of a prepotent response and interference control (Barkley, 1997). Inhibitory deficits, in particular during those tasks requiring inhibition of motor responses, are the most consistent and replicated findings in children with ADHD.

Motor inhibition processes are typically measured using the Go/NoGo (GNG) task or the Stop Signal Task (SST). Both involve the inhibition of a motor response; however, they have significant differences. In the GNG task, Go and NoGo stimuli requiring different responses (Go- press button/ NoGo- do not press) are presented pseudorandomly to the subject. The typically high proportion of Go trials (at least 70%) compared to the much lower proportion of NoGo trials elicits a highly prepotent response tendency (and inhibitory load), which increases with proportion of Go trials included in the task. Thus, this paradigm involves selective attention, response selection and response inhibition. On the other hand in the SST, the Stop signal is presented with a variable delay after the presentation of the Go signal, therefore the response has already been triggered and the subject has to inhibit a motor response that is on its way of execution. Thus, this paradigm has a higher load on motor response inhibition processes than the GNG task (Eagle, Bari, & Robbins, 2008; Rubia, Russell, et al., 2001).

The “race” model of behavioural inhibition as described by Logan et al (Logan, Schachar, & Tannock, 1997) proposes the “go” and “stop” processes as independent of one another, and describes the “race” that occurs between the two of them for completion after the presentation of a Stop signal. If the Stop process can overtake the Go process, the subject will be able to inhibit the response (Logan et al., 1997). The dependent variable is the probability of inhibition, which is sometimes also presented as commission errors. The Stop Signal Reaction Time (SSRT; time needed for inhibition to be successful after the presentation of a stop signal), is considered to be the main indicator of the efficiency of the inhibitory processes. In the traditional version of the Stop task, the Stop Signal Delay (SSD) is constant and the SSRT is calculated as the RT in the *n*th rank-ordered distribution of RTs minus the

SSD (where the SSD is fixed and *nth RT* is defined by the product between the number of RTs in the distribution and the probability of responding to the Stop signal) (Oosterlaan & Sergeant, 1998). However, in more recent studies the SSD is individually adjusted depending on the performance of the subject so as to ensure 50% of successful inhibitory trials (Logan et al., 1997; Rubia, Smith, et al., 2007a). In this version, the SSRT is usually calculated as the average of the RT to Go signals (MRT Go) minus the average of the Stop Signal Delay (SSD) (Logan et al., 1997).

Neuropsychological studies have consistently shown that children with ADHD compared to healthy controls perform worse in both motor response inhibition tasks. Meta-analytic studies have shown that children with ADHD have longer SSRTs than healthy controls (Alderson et al., 2007; Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Nigg et al., 2005; Willcutt et al., 2005), also observed in later studies (de Zeeuw et al., 2008; Epstein, Langberg, et al., 2011; Lee et al., 2008; Martel, Nikolas, & Nigg, 2007; Rommelse et al., 2008; Rubia, Smith, et al., 2007a).

Commission errors during motor inhibition tasks (responses to NoGo/ Stop stimuli) are traditionally interpreted as reflecting impaired inhibitory control, whereas omission errors (no responses to go stimuli) may be interpreted as a sign of attention deficits (Rubia, Smith, et al., 2007a). Children with ADHD compared to healthy controls have shown consistently an increased number of commission errors during GNG tasks (Rubia, Smith, et al., 2007a; Rubia, Taylor, et al., 2001; Slaats-Willems, Swaab-Barneveld, de Sonneville, van der Meulen, & Buitelaar, 2003; Wodka et al., 2007) and SST (Bedard et al., 2003; Huang-Pollock, Mikami, Pfiffner, & McBurnett, 2007; Oosterlaan et al., 1998; Overtom et al., 2002; Rommelse et al., 2008; Rubia et al., 1998; Solanto et al., 2001; Stevens, Quittner, Zuckerman, & Moore, 2002). However, also increased omission errors, suggestive of attention deficits, have been reported during GNG tasks (Kerns et al., 2001; Klein et al., 2006; Rubia, Taylor, et al., 2001; Wodka et al., 2007) and SST (Klein et al., 2006).

Furthermore, the deficits observed in ADHD during motor response inhibition have shown their independence of any working memory or reward manipulations of the task (Wodka et al., 2007), which according to the authors suggests a primary role for impaired inhibition in ADHD (Wodka et al., 2007).

Nevertheless, there are also studies where no differences on inhibitory indexes have been observed between children with ADHD and healthy control subjects (Kerns et al., 2001; Rhodes et al., 2005; Scheres, Oosterlaan, & Sergeant, 2001). However,

this may have been influenced by differences in the design of the paradigms. As an example, in the study from Rhodes et al (Rhodes et al., 2005), their GNG task had the same percentages of Go and NoGo signals (50%), thus having less inhibitory load than other versions which as mentioned above typically include at least 70% Go trials to elicit a strong prepotent response.

1.2.1.2 Interference inhibition deficits

Children with ADHD have also shown impaired performance in other tasks that involve inhibitory processes with however, less consistent results. Interference inhibition is defined as the ability to ignore irrelevant information that interferes or competes with the processing of relevant information. To assess this, the most widely used tasks are the Stroop (Golden, 1978), Simon (Simon, 1990) or the Flanker (Eriksen & Schultz, 1979) tasks. While in the Flanker task, the participants have to ignore other stimuli that interfere with the relevant characteristic of the target stimulus, in the Stroop and Simon tasks, participants have to a) ignore a feature of the target stimulus that is providing irrelevant information, and b) focus on the relevant characteristic, necessary to perform the task.

Recent studies have also mostly failed to find differences during interference inhibition between children with ADHD and healthy controls using variations of the Stroop (Brocki, Randall, Bohlin, & Kerns, 2008; van Mourik et al., 2009; van Mourik, Sergeant, Heslenfeld, Konig, & Oosterlaan, 2010), Simon (Rubia, Smith, et al., 2007a; van Mourik et al., 2009) or the Flanker tasks (Adolfsson, Sorensen, & Lundervold, 2008; Booth, Carlson, & Tucker, 2007; Yordanova et al., 2011), although some positive findings have also been reported, with more errors and increased MRT observed in children with ADHD compared to healthy peers (Gualtieri & Johnson, 2006; Johnson, Robertson, et al., 2008; for meta-analyses of results during Stroop tasks, see Lansbergen et al., 2007; for a meta-analysis of results during Simon and Flanker tasks, see Mullane et al., 2008; Mullane, Corkum, Klein, McLaughlin, & Lawrence, 2010; and van Mourik, Oosterlaan, & Sergeant, 2005), and one meta-analytic study reported a weighted effect size of 0.75 (Homack & Riccio, 2004).

1.2.1.3. Cognitive inhibition deficits

Different paradigms have been used to assess cognitive inhibition, cognitive flexibility or cognitive switching, such as the Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948) or the intra-dimensional/extra-dimensional set-shifting tasks (Kempton et al., 1999). These paradigms typically require from the participants to identify a classification criteria that changes unexpectedly, and therefore they must inhibit their current responses, change the criteria they are following to respond and adjust their responses according to this new classification criteria.

Findings from studies using these tasks are less consistent than those for motor inhibition tasks. Willcutt et al in their meta-analytic review observed impaired performance in ADHD patients compared to controls during the WCST (Willcutt et al., 2005). However, no differences (Goldberg et al., 2005; Happe, Booth, Charlton, & Hughes, 2006) or differences with small effect sizes during ID/ED tasks (Gau & Shang, 2010a; Rhodes et al., 2005) have also been reported. Other studies using simpler switch task versions that had a lower load on working memory functions have also shown inconsistent effects. Children with ADHD compared to healthy controls have shown fewer correct responses and more errors during a shifting attention test (Gualtieri & Johnson, 2006) and, in another study using a simple visual-spatial cognitive switching paradigm, a trend for higher Switch cost in children with ADHD compared to healthy participants was reported (Rubia, Smith, et al., 2007a). When interpreting these findings it is necessary to consider that these paradigms however typically co-measure other cognitive processes, most prominently, attention functions but also working memory (in particular during the WCST) whose effect on the performance of the subject may be difficult to disentangle.

It can therefore be concluded from the evidence that children with ADHD show deficits during inhibitory processes. The evidence is very consistent with regards to the deficits in motor response inhibition tasks, particularly when measured using the SSRT and commission errors during the GNG. However, it cannot be overlooked that also omission errors, suggestive of attention difficulties, have been reported.

The evidence is not that conclusive with regards to interference inhibition or cognitive switching. Mixed results have been reported during interference inhibition tasks, as shown by different meta-analytic studies. Similarly, mixed results have been

reported during cognitive flexibility tasks: during complex tasks loading also on working memory processes, small effects have been reported however, deficits have been reported during simpler switching tasks.

It is important to note here that although paradigms are typically designed to isolate the cognitive process studied, other cognitive processes unavoidably co-occur. Thus, sustained attention is necessary to perform all the inhibitory tasks mentioned in this chapter. Depending on the task, other processes may be heavily involved, like selective attention or attention allocation, which are very prominently engaged in particular during interference inhibition tasks and to some extent also during cognitive inhibition tasks. Hence, the design of the paradigm is crucial to be able to detect potential deficits, as well as to correctly identify the cognitive process impaired in that population.

Differences in the paradigms used may underlie part of the discrepancies reported however, the evidence suggests that the use of motor response inhibition tasks may be particularly sensitive to the inhibitory deficits presented by children with the disorder.

1.2.2. Sustained attention deficits

Sustained attention can be defined as the ability to voluntarily maintain the focus of attention to critical but infrequent events (Parasuraman, Warm, & See, 1998; Warm, 1984), but it has also been defined as a decrement of vigilance/sustained attention over time, which has been influential in the ADHD literature (Sergeant, 1996).

The Continuous Performance Test (CPT) is typically used to measure sustained attention (Conners, 1993). In its simplest version, subjects are presented a stream of letters, and they have to respond only to one of them (e.g. X). Variations of the task have also been used, and thus in the CPT A-X version subjects have to respond to every “X” only when it has been preceded by the letter “A”. During these tasks, commission errors are typically interpreted as an index of impulsive difficulties, and omission errors as a sign of attention problems (Epstein et al., 2003; Halperin et al., 1988).

A classic meta-analytic review by Losier et al (Losier, McGrath, & Klein, 1996) showed that children with ADHD made more commission and omission errors than comparison subjects (Losier et al., 1996). This was also observed in a more

recent meta-analytic review where the majority of the reviewed studies that included sustained attention paradigms observed between-group performance differences, with children with ADHD making more omission and commission errors than healthy subjects (Willcutt et al., 2005). More recent studies have also confirmed these deficits. Using the CPT, children and adolescents with ADHD compared to healthy controls have shown an increased number of commission and omission errors (Epstein et al., 2003; Gualtieri & Johnson, 2006; Huang-Pollock et al., 2006; Kerns et al., 2001; Klein et al., 2006; Rubia, Smith, et al., 2007a).

A deterioration of performance over time has also been reported. Thus, Huang-Pollock et al reported a worsened performance in the task over time, with a significantly increased number of errors and slowed RT with increased time on task (Huang-Pollock et al., 2006). In the Sustained Attention to Response Task (SART) (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) subjects are shown numbers (1-9) presented to them in a predictable and repeated sequence, and they are required to respond to every number but one (e.g. “3”). During this task, children with ADHD have shown more omission (Johnson et al., 2007; Yang et al., 2007) and commission errors (Johnson et al., 2007) compared to healthy peers, as well as an increased fast trail-to-trial RT variability and a significant slowing of their RT over the task (Johnson et al., 2007). They showed no change in the number of omission or commission errors over time, but deficits were observed from the start, which according to the authors is suggestive of deficits in sustained attention over short periods of time, reflective of fronto-parietal dysfunction, whereas the progressive slowing in RT may be due to a decrease in arousal levels potentially involving noradrenergic system (Johnson et al., 2007).

Thus, children with ADHD have consistently shown deficits during sustained attention tasks, both with regards to the number of omission errors and deterioration of performance with time, but also on the impulsivity measures of the task, with an increased number of commission errors being consistently reported.

1.2.3. Working memory deficits

Working memory (WM) refers to a limited capacity system that allows for the temporary storage and manipulation of information, necessary to guide behaviour (Baddeley, 1996). Thus, it allows for the behavioural independence from environmental cues, given the internal representation of information guides the

behaviour of the subject for future actions (Baddeley, 1996). Baddeley's model of WM describes two slave systems, the phonological loop and visuo-spatial sketchpad, controlled by a modality-free central executive. Deficits in WM have been hypothesised as a core deficit in ADHD (Castellanos & Tannock, 2002). However, the variety and complexity of the tasks used make difficult the interpretation of the findings.

Verbal-auditory WM is typically measured by tasks such as the Forward/Backward Digits Span task, the California Verbal Learning Test (CVLT), or the N-Back task. In the Digit Span task, series of digits are sequentially presented to the participant, digits that have to be recalled in the correct order (forward/backwards). In the CVLT, participants are presented paired words, which they have to learn and recall immediately and after a 20 minutes delay interval. In the N-Back task, series of letters are presented to the subject one by one. In the conditions "1-back", "2-back" and "3-back", the subject has to press the button whenever the letter presented on the screen is the same as the letter one, two or three before it, respectively. To measure visuo-spatial WM, the Corsi Blocks (Milner, 1971) or variations of this tasks are traditionally used. In this task, nine blocks are irregularly distributed over a black/wooden board and the subject has to tap out exactly the same sequence pattern as previously shown by the examiner.

Children with ADHD compared with controls have shown deficits in performance during tasks measuring verbal-auditory and visuo-spatial WM in different meta-analytical studies (Martinussen et al., 2005; Willcutt et al., 2005). As described by Martinussen et al. (Martinussen et al., 2005), the larger effect sizes observed in visuo-spatial WM tasks when compared to verbal-auditory WM tasks may be due to visuo-spatial tasks being more challenging than verbal-auditory tasks or involving less automated or familiar material, or maybe due to the influence of potential comorbidities such as developmental coordination disorder. Furthermore, they show the moderator role of the presence of reading difficulties or learning impairment not only in the results of those tasks tapping on verbal-auditory WM but also on visuo-spatial WM tasks (Martinussen et al., 2005). More recent studies have also observed deficits in visuo-spatial WM in children with ADHD compared to healthy controls (Gau & Shang, 2010a; Rhodes et al., 2005; Rhodes, Park, Seth, & Coghill, 2011; Rommelse et al., 2008; Toplak, Jain, & Rosemary, 2008; Yang et al., 2007) even in preschoolers (Re, De Franchis, & Cornoldi, 2010).

Impairments in verbal-auditory WM have also been described in later studies. During the CVLT, children with ADHD compared to control peers have shown impaired performance in the number of words recalled after temporal delay (Crocker, Vaurio, Riley, & Mattson, 2011), and reduced accuracy was reported during the Digit span test (Rommelse et al., 2008; Toplak et al., 2008).

Using the N-Back task, children with ADHD have shown an enhanced number of omission errors (Klein et al., 2006). In a modified version of the N-Back task, children with ADHD showed worse performance than healthy controls in both a visual-object version and a phonological version (Pasini et al., 2007).

Thus, the available evidence supports the presence of deficits in verbal-auditory and visuo-spatial WM in children with ADHD, despite the variety of tasks used.

1.2.4. Temporal processing deficits

Impulsivity is conceptualised as a behavioural style which is premature and inadequate, where responses are made too early, inaccurately and without consideration of the consequences (Rubia et al., 2000; Smith, Taylor, Rogers, Newman, & Rubia, 2002). Deficits in temporal processes have been hypothesized as one of the key neuropsychological underpinnings for the impulsiveness typically observed in children with ADHD (Rubia, Halari, Christakou, et al., 2009).

Different tasks are used to assess the presence of temporal processing deficits: a) motor timing tasks (sensorimotor synchronization/ anticipation in the milliseconds or seconds range); b) time perception tasks (time discrimination of short intervals in the seconds/milliseconds range; verbal time estimation, temporal production, time reproduction) and c) temporal foresight or temporal discounting tasks (gambling or temporal discounting) (Rubia, Halari, Christakou, et al., 2009). Temporal anticipation tasks require from the subject the prediction of the onset of an upcoming stimulus. During sensorimotor synchronization tasks, participants have to adjust their motor response to externally timed sensory stimuli in finger tapping tasks. During time estimation tasks, participants may have to give a verbal estimate of the duration of a specific stimulus, whereas during time production/reproduction tasks they have to (re)produce specified time periods precisely. Time or duration discrimination tasks require from the participants the discrimination of temporal intervals which differ in their duration in the order of milliseconds to seconds.

As described in the review by Toplak et al (Toplak et al., 2006), the methods vary significantly between studies, and therefore no meta-analysis has as yet been conducted. Nevertheless, the evidence supports the presence of deficits during duration discrimination tasks, duration reproduction and finger tapping tasks, and less consistently have been reported differences on verbal temporal estimation and anticipation tasks (Rubia, Halari, Christakou, et al., 2009; Toplak et al., 2006).

During sensorimotor synchronization tasks, children with ADHD showed impaired performance (Ben-Pazi, Gross-Tsur, Bergman, & Shalev, 2003; Gualtieri & Johnson, 2006; Landau, Auerbach, Gross-Tsur, & Shalev, 2003; Pitcher, Piek, & Barrett, 2002) and increased intra-individual variability relative to healthy subjects (Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003; Rubia, Taylor, Taylor, & Sergeant, 1999; Toplak & Tannock, 2005a). These findings suggest the presence of difficulties to adjust the timing of their motor responses. However, some studies have also shown negative results (Aase & Sagvolden, 2006; Tiffin-Richards, Hasselhorn, Richards, Banaschewski, & Rothenberger, 2004; see Toplak et al., 2006 for a review).

Children with ADHD did not differ from controls in a time production task where they had to give a verbal estimate of 10 secs duration (Smith et al., 2002), although it has recently been reported that children with ADHD compared to healthy controls underestimated time intervals of 6, 12 and 24 secs but not shorter intervals of 1 and 3 secs (Huang et al., 2012). Under-reproduction of time intervals, which suggests that time is subjectively elongated to these children, has been observed during tasks of time reproduction, where youths with ADHD compared to healthy peers were reported to display significant deficits, which were more marked as difficulty increased (longer duration of stimuli) (Gonzalez-Garrido et al., 2008; Huang et al., 2012; Hwang, Gau, Hsu, & Wu, 2010; Luman et al., 2008; Plummer & Humphrey, 2009; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007; Smith et al., 2002; Valko et al., 2010). These deficits were observed both when stimuli are auditory and visually presented (Rommelse et al., 2007), although there is some evidence for more severe impairments when visually presented (Plummer & Humphrey, 2009). However, negative results have also been reported (Toplak et al., 2003).

Small and longer time durations are processed differently, possibly due to the greater load on working memory, sustained attention to time and inhibition of the interference as temporal intervals increase (Smith et al., 2002). These factors may

influence performance during time production and reproduction tasks, but would not affect performance in a duration discrimination task, where seconds-long intervals that differ by several hundreds of milliseconds need to be discriminated (Smith et al., 2002). Thus, to avoid these potential confounds, several studies have investigated the presence of deficits in children with ADHD during temporal discrimination tasks. Children with ADHD compared to healthy controls have shown difficulties to discriminate between durations that differed between 250-450 ms, needing larger interval duration to discriminate durations accurately (Rubia, Smith, et al., 2007a; Smith et al., 2002; Valko et al., 2010). Similarly, children with ADHD compared to healthy controls required higher thresholds to discriminate durations at short (300ms), median (800 ms) and long (1200ms) durations, which was specially marked in the long intervals (Huang et al., 2012; Yang et al., 2007). Toplak and Tannock reported duration discrimination deficits which were especially prominent when stimuli were visual, observed at short (200ms) and long (1000 ms) intervals (Toplak & Tannock, 2005b). Finally, Himpel et al (Himpel et al., 2009) have shown that children with ADHD performed significantly worse than healthy controls in a time discrimination (TD) task in very short (50ms) and longer (1000ms) stimuli durations.

The interdependence between different cognitive functions, although mentioned in a previous section of this chapter, needs to be mentioned again here. Temporal discounting tasks require participants to choose between variable smaller immediate or larger delayed rewards and thus assess the subjective value of reward as a function of its delayed administration (Richards, Zhang, Mitchell, & deWit, 1999). Thus, the task requires reward-related decision making processes, but also temporal processes (i.e. temporal foresight to consider the future reward) and sustained attention, and the influence of each of these cognitive processes in the performance of the subject during the task is difficult to disentangle.

Children with ADHD have shown an enhanced preference for small immediate versus larger delayed rewards and less advantageous performance than that of healthy comparison subjects during different versions of temporal discounting tasks (Antrop et al., 2006; Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009; Marco et al., 2009; Scheres, Lee, & Sumiya, 2008; Scheres, Tontsch, Thoeny, & Kaczurkin, 2010; Solanto et al., 2001; Toplak et al., 2008; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2011)(for reviews see (Luman et al., 2005; Luman et al., 2010)),

although some studies have found no between group differences (Scheres et al., 2006).

Delay-aversion has been considered as the observable consequence of time perception deficits (Rubia et al., 2009), result of a “fast internal clock” during waiting periods (Sonuga-Barke, Saxton, & Hall, 1998) or increased susceptibility to the passage of time due to an elongated subjective time sense (Rubia, Halari, Christakou, et al., 2009). In a study by Antrop et al (Antrop et al., 2006), performance differences disappeared when visual stimulation between stimuli and response was introduced, thus making the delays more tolerable for children with ADHD (Antrop et al., 2006). However, whether the main deficit observed during these tasks in children with ADHD is the abnormal sensitivity to reward itself, the hypersensitivity to the passage of time (temporal processing deficits), or both still needs to be elucidated (Rubia, Halari, Christakou, et al., 2009). Furthermore, timing deficits have been recently considered as a potential separate pathway to ADHD (Sonuga-Barke et al., 2010), with the strongest familial effects observed in the inhibition and timing factors rather than in delay-aversion factor (Sonuga-Barke et al., 2010).

Thus, evidence is suggestive of deficits in temporal processes. The most consistent deficits have been observed a) during time discrimination tasks, when stimuli have a duration of approximately 1 second and differ between them by hundreds of milliseconds and b) during time reproduction and estimation tasks, in particular during longer time intervals. The observed impairment during time discrimination tasks supports the presence of pure time perception deficits, given their minimum motor component and relatively low working memory load.

1.3. Summary and conclusions

Findings from neuropsychological studies in ADHD show consistent evidence for the presence of impaired motor response inhibition, temporal processing, working memory and sustained attention. With respect to deficits in interference inhibition or cognitive flexibility the results are less consistent. Furthermore, ADHD patients have also shown deficits in temporal discounting and other reward-related tasks. Whether this is due to abnormal sensitivity to reinforcers or to abnormal sensitivity to the temporal delay period typically involved in these paradigms still needs further research.

However, children with ADHD show a significant heterogeneity in the observed deficits in EF (Nigg et al., 2005; Sonuga-Barke et al., 2010), with some children not being impaired, and further research is necessary investigating subtypes of ADHD. Many of the studies reviewed include subjects with different subtypes of ADHD, collapsing these in the analyses (Gau & Shang, 2010a; Huang et al., 2012; Johnson et al., 2007; Klein et al., 2006; Luman et al., 2008; Rubia, Smith, et al., 2007a; Toplak et al., 2003; Toplak et al., 2008; Wodka et al., 2007; Yang et al., 2007). Most frequently, studies include only the combined and predominantly inattentive subtypes and exclude the hyperactive subtype whose validity has been questioned, as it is less frequent in adolescence (Froehlich et al., 2007; Merikangas et al., 2010) and has been considered as a potential precursor of the combined subtype (Barkley, 1997; Lahey, Pelham, Loney, Lee, & Willcutt, 2005). There is a high degree of overlap between the inattentive and combined subtypes (Lee et al., 2008), as both share above-threshold symptoms in one dimension (inattention domain) and differ in the level of symptoms in a second dimension (hyperactive/impulsive). In this second dimension, the combined subtype presents with more than 6 symptoms, and the inattentive subtype falls below the 6 symptoms' cut-off (American Psychiatric Association, 2000). Therefore, children with the combined subtype would theoretically be more impaired as they display a higher total number of symptoms. However, the different studies typically do not provide a detailed description of the characteristics of the children included in the inattentive subgroup such as their number of symptoms/ hyperactivity levels. The predominantly inattentive group could include children who fell short of hyperactive/impulsive behaviours as to receive the diagnosis of combined subtype, as well as those who are more purely inattentive and show an inattentive sluggish tempo (Stefanatos & Baron, 2007). Thus, the inclusion of both subtypes in the studies may lead to heterogeneous results. Furthermore, some authors have suggested that motor inhibition deficits may be more associated with the combined subtype (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). However, several studies showed that are symptoms of inattention rather than those of hyperactivity are associated with impaired inhibitory measures (Chhabildas, Pennington, & Willcutt, 2001; Huang-Pollock et al., 2007; Willcutt et al., 2005), or with deficits in EF (Martel et al., 2007). Therefore, the debate about whether or not the combined and predominantly inattentive subtypes are etiologically similar or distinct entities (Barkley, 2001; Hinshaw, 2001; Milich, Balentine, & Lynam, 2001;

Swanson et al., 2007) is not as yet resolved. Given the significant symptomatic overlap between subtypes (Lee et al., 2008), which is unlikely to be solved by the new version of the classification system DSM-V, a better definition of the subgroups recruited that increase the homogeneity of the sample is required in future studies. In order to increase the homogeneity of the sample, in this study we only included children with a diagnosis of ADHD combined subtype.

Another issue is the lack of specificity of the deficits (Lipszyc & Schachar, 2010; Sergeant, Geurts, & Oosterlaan, 2002), as none of the deficits observed in ADHD populations is specific or unique to this disorder. Furthermore, the inclusion of subjects with comorbid disorders (Gau & Shang, 2010a; Goldberg et al., 2005; Huang et al., 2012; Johnson et al., 2007; Klein et al., 2006; Luman et al., 2008; Martel et al., 2007; Pasini et al., 2007; Rhodes et al., 2005; Rubia, Smith, et al., 2007a; Smith et al., 2002; Toplak et al., 2003; Toplak et al., 2008; Wodka et al., 2007; Yang et al., 2007) may confound the findings of cognitive deficits in children with ADHD, even when comorbidity is restricted to comorbid conduct disorder (CD) or oppositional defiant disorder (ODD), as it has been shown to have an additive effect on the cognitive deficits observed in ADHD (Rhodes et al., 2011). Studies where the contribution of comorbid conditions to the observed deficits can be ruled out are therefore required. In this PhD we tried to include mostly non-comorbid patients. However, two patients presented with a confirmed diagnosis of comorbid CD/ODD.

Another aspect that increases the heterogeneity of the samples and therefore complicates the integration of the findings is the inclusion of girls and boys in the samples, collapsing their results (de Zeeuw et al., 2008; Epstein, Langberg, et al., 2011; Gau & Shang, 2010a; Goldberg et al., 2005; Huang et al., 2012; Klein et al., 2006; Luman et al., 2008; Martel et al., 2007; Smith et al., 2002; Solanto et al., 2001; Toplak et al., 2003; Toplak et al., 2008; van Mourik et al., 2009; Yang et al., 2007). Some authors have shown differential cognitive deficits suggesting different cognitive profiles depending on gender (Balint et al., 2009; Nigg et al., 2002), which is in line with observed gender-related differences in brain function, presentation of the disorder and brain maturation (De Bellis et al., 2001; Gershon, 2002; Mahone & Wodka, 2008; Rubia, Hyde, Halari, Giampietro, & Smith, 2010; Valera et al., 2010). Therefore, the inclusion of males and females may mask or attenuate differences that, should the samples have been gender-homogeneous, would have been present. To

avoid heterogeneity due to gender, in this PhD we therefore included only male patients and controls.

It is also necessary to take into account the effect of the inclusion of children with ADHD who had a previous history of stimulant medication. Few studies have included medication naïve samples (Epstein, Langberg, et al., 2011; Pasini et al., 2007; Rhodes et al., 2005; Rhodes et al., 2011; van Mourik et al., 2009; Yang et al., 2007). Given its observed long-term effects on brain structure and function (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2007; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Shaw, Sharp, et al., 2009), this may have had an impact on the findings, which need to be interpreted with caution. Therefore, in this PhD only medication naïve patients were included in order to avoid any confounds related to long-term effects of stimulant medication

Finally, it is necessary to highlight the key role of the correct design of the paradigm on the study of the cognitive deficits associated with any disorder. Ideally, paradigms should facilitate the measure of isolated cognitive functions without the potential confound of other functions interfering in the performance of the task. However, as it has been reviewed, different variations and modifications of the paradigms have been used, which complicate the interpretation and replication of the findings.

Therefore, it can be concluded that despite the limitations, the reviewed evidence supports the presence of cognitive deficits in children with ADHD in motor inhibition, temporal processing and working memory processes. However, not all the children with the disorder show cognitive deficits, but different subgroups of children with ADHD show differential neuropsychological profiles (Nigg et al., 2005; Sonuga-Barke et al., 2010). The role of these differential cognitive profiles in the symptomatic manifestation of the disorder still needs to be elucidated. Studies with more well-defined, homogeneous, non-comorbid, medication-naïve samples are required.

CHAPTER 2. STRUCTURAL AND FUNCTIONAL BRAIN IMAGING IN ADHD

The previous chapter has reviewed the evidence from neuropsychological studies in ADHD, which have shown that children with ADHD have deficits in a range of cognitive functions including motor response inhibition, working memory and temporal processing, as well as deficits in sustained attention and delay of gratification. Early descriptions of the disorder already included references to the lack of control and impulsivity problems presented by these children, symptoms of hyperactivity, impulsivity as well as those of inattention whose biological aetiology was also very early hypothesised to be associated with abnormal brain structure and/or function (for reviews, see Lange, Reichl, Lange, Tucha, & Tucha, 2010; Taylor, 2011). Thus, the biological aetiology of the disorder is either explicitly or indirectly implied in Still's descriptions of "defect of moral control", the concept of "Minimal Brain Damage" or "Minimal Brain Dysfunction", as well as in the description of Kramer and Pollnow of "hyperkinesis of childhood" (Lange et al., 2010; Taylor, 2011), all of them very close to the symptomatic description of ADHD as we know it today. Furthermore, lesion studies as well as the encephalitic lethargica epidemic that affected the world in the 1920's helped to confirm the connection between abnormalities in brain structure or dysfunction and behavioural symptoms of hyperactivity, impulsivity and deficits in attention, as these patients showed symptoms and cognitive deficits similar to those displayed by children with ADHD (Lange et al., 2010; Mattes, 1980; Taylor, 2011).

The development of modern brain imaging techniques has allowed neurosciences to provide accurate evidence on the association between brain abnormalities and cognition or symptoms, evidence that has grown exponentially since the development of the first Computerised Tomography (CT) scan by the British electric engineer Sir Godfrey Hounsfield in the mid-70s (Ambrose & Hounsfield, 1973; Hounsfield, 1973). This meant a significant step forward on the study of the abnormalities of the human brain, which moved from lesion and post-mortem studies, or the use of X-rays and angiography methods, to the modern methods of brain imaging developed mostly in the last 40 years: CT scanning and structural Magnetic Resonance Imaging (see (Hoeffner, Mukherji, Srinivasan, & Quint, 2012) for a review). The development of modern structural and functional imaging techniques has

changed completely the way clinicians and researchers have been able to determine the association between basic and higher cognitive functions and neural tissue, with a particularly remarkable impact on those sciences whose main focus is the brain and its structural and functional abnormalities, such as, Neurology and Psychiatry.

The next section will provide a brief review of the basic concepts underlying the most commonly used structural and functional brain imaging methods. This will be followed by the review of the evidence provided by these techniques on structural and functional brain abnormalities in ADHD.

2.1 Structural and functional brain imaging methods

2.1.1. Methods used for the study of brain structure

CT-scans and Magnetic Resonance Imaging (MRI) scanning allow obtaining three dimensional (3-D) structural brain images of a given subject. CT-scanning is based in the use of X-rays and the different densities of the tissues in the brain (Ambrose & Hounsfield, 1973; Hounsfield, 1973), information which is captured and used by the CT-scan to create a 3-D image of the brain studied.

MRI (Damadian, 1971; Mansfield et al., 1980) is based on the magnetic properties of the different components of the brain. Protons in different tissues have different magnetic properties. The MRI scan has a determined strong static magnetic field (e.g. 3 Tesla), which aligns all the magnetically sensitive particles in that direction (for reviews, see Banich, 2004; Higgins, Platts, & Pickman, 1996). Thus, when the subject is placed inside the scan, the protons present in the different tissues of the brain will align in that direction. The subject then receives short radio-frequency pulses that affect the magnetic alignment of the protons in a determined tissue to align with the new magnetic force. The time it takes these protons to re-align again to the magnetic field of the scan are the “relaxation times” (T1 and T2), which provides the scan with the information to reconstruct a 3-D image of the studied brain (Higgins et al., 1996). The main advantages of MRI compared to CT scans are the better spatial resolution and the fact that it does not involve X-rays. However, because the scanner contains a very big and strong magnet, it cannot be used in some cases (i.e. metal in their bodies). Furthermore, because of the small space inside the scan, it can be claustrophobic.

Diffusion Tensor Imaging (DTI) techniques (Basser, Mattiello, & LeBihan, 1994), based on water diffusion characteristics, allow for the measurement of anatomical connectivity between brain regions. DTI fiber tracking provides several indexes of water diffusion in white matter tracts (Assaf & Pasternak, 2008), thus providing information not only about macrostructural characteristics of white matter tracts (which tracts connect which brain areas) (Assaf & Pasternak, 2008; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004), but also (indirectly) about the microstructural characteristics of these tracts (their integrity of the white matter tracts) (Beaulieu, 2002).

However, these techniques (CT scans, MRI, DTI) cannot provide us with information about brain function, but only about potential brain structure abnormalities.

2.1.2. Functional Magnetic Resonance Imaging

The development of functional magnetic resonance imaging (fMRI) techniques in the early 90s (Kwong et al., 1992; Ogawa, Lee, Kay, & Tank, 1990) allowed for the study of brain function. It takes advantage of the MRI technique described above, and the different magnetic properties of oxygen-rich and deoxygenated blood. Oxygen-rich blood is diamagnetic, whereas deoxygenated blood is paramagnetic and influences the magnetic field of the neighbouring protons (Ogawa et al., 1990). When neurons are active, they consume oxygen, and as a result of their increased need for oxygen, there is a local increase on rich-oxygenated blood supply which exceeds the needs of that brain region (Fox & Raichle, 1986), therefore increasing the ratio oxygenated/deoxygenated blood (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Fox & Raichle, 1986). Making use of the different magnetic properties, fMRI scans measure this increase in the ratio oxygenated/deoxygenated blood while a brain area is active compared to when it is not, which is taken as a baseline (Bandettini et al., 1992; Ogawa et al., 1990). This is the so called Blood Oxygen Level Dependent (BOLD) signal (Ogawa et al., 1990). The accurate interpretation of changes in BOLD signal depends on the understanding of the way neural activity produces changes in haemodynamic response, known as neurovascular coupling (Arthurs & Boniface, 2002). Changes in BOLD signal are thought to reflect neural activity associated with the input and local processing rather than output activity (Lauritzen & Gold, 2003; Logothetis, 2002; Logothetis & Wandell, 2004).

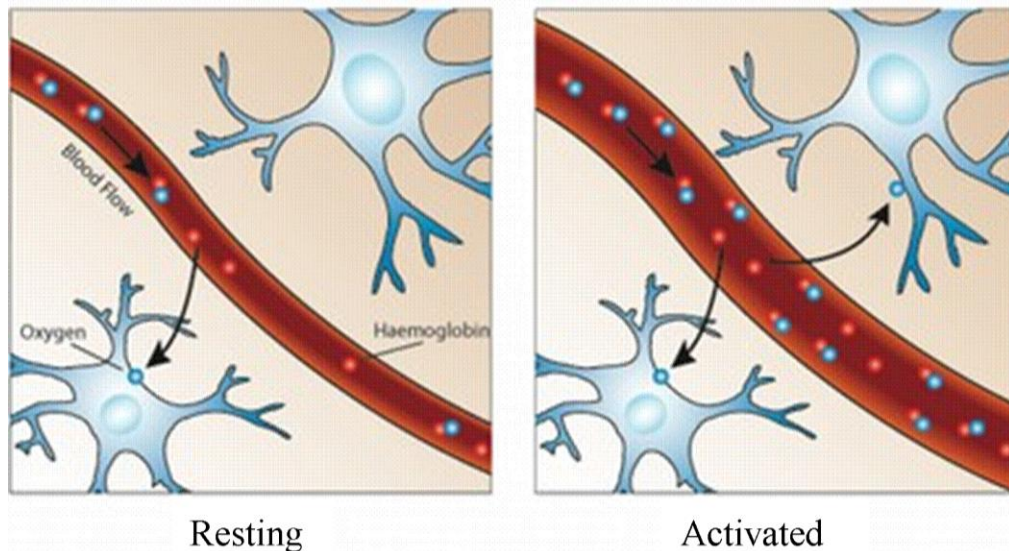


Figure 2.1. Changes in oxygenated/deoxygenated ratio, origin of the BOLD signal in fMRI. The proportions of oxygenated (tandem blue+red circles)/ deoxygenated (single red circles) blood in the blood flow is increased as a consequence of increased neuronal activity. Image from <http://psychcentral.com>

This has an important implication, as we are measuring an increase, a difference between two situations. Thus, to identify brain areas associated with increased neuronal activity during a given cognitive process as measured by a cognitive task, typically a control task is being subtracted from the task of interest, that controls for all functions that are not the interest of the study. For example, in an inhibition task, the control task would contain the same visual stimulation and motor response as the active task, but not the inhibitory process itself, which would be subtracted out, by the contrast of the active versus the control task (Gusnard & Raichle, 2001; Logothetis, 2008). The key concept therefore is “subtraction”: fMRI data analyses subtract that activation related to the baseline condition from the signal observed during the condition of interest. By doing this, fMRI does not provide with an absolute measure of brain activity but only with the relative regional increase of oxygenated blood supply, an indirect measure of brain activation. Therefore, the design of the task is of utmost relevance when using subtraction methods. The better matched the tasks for all conditions of no interest, the better the function of interest can be isolated. However, the subtraction method is not perfect. It is important to note that the different cognitive processes do not follow strictly an additive model but interact with each other, and therefore even the best baseline task will not allow for the absolute isolation of the cognitive process of interest.

Using fMRI, we are not obtaining a direct measure of brain activation, but only a relative measure of changes in hemodynamic response compared to a previous baseline, which is one of the main drawbacks of the technique. This hemodynamic response is furthermore not immediate but takes between 4-6 seconds to peak (Huettel & McCarthy, 2000), which also needs to be taken into account when interpreting BOLD images, as neural events happen in the milliseconds range, while the hemodynamic response occurs with a delay of several seconds.

2.1.3. Other methods used for the study of brain function

Electroencephalography (EEG) and Event-Related Potentials (ERPs) allow for the study of the electrical fields resulting from neural firing in the participants, with a temporal resolution within the milliseconds range (Gruzelier, Burgess, & Baldeweg, 1996; Luck, 2005). EEG allows for the measurement of the electrical activity resulting from neural firing by using electrodes placed on the scalp of the subject (Coles & Rugg, 1995). The voltage and the frequency of the recorded electric activity provide a continued measure of brain activity (Gruzelier et al., 1996). ERPs record brain activity elicited by an event, and by analysing the changes in the components of the waveform recorded on the scalp it can provide information about different cognitive processes, their temporal course and their potential disturbances in the milliseconds range (Banich, 2004; Coles & Rugg, 1995). Both EEG and ERPs are relatively inexpensive compared to other techniques and have an excellent temporal resolution. However their main drawback is the comparatively reduced spatial resolution, as it is difficult to locate the exact origin of the recorded activity, especially when it comes to deep brain structures (Gruzelier et al., 1996; Luck, 2005).

Magnetoencephalography (MEG) (for a review, see Andrews, 1996) allows for the detection and recording of the magnetic fields associated with the electric activity of the neurons (Banich, 2004; Otsubo & Snead, 2001).

Positron Emission Tomography (PET) is very versatile and can measure brain activity in the form of blood flow, glucose utilisation or the distribution of neurotransmitter receptors and transmitters (Sokoloff, 1977). Radioactive agents, denominated radioligands or radiotracers, are administered to the subject typically intravenously as a bolus and, once inside the blood flow, they reach the brain and are taken by the neurons as the non-ionized form of the molecules (Banich, 2004; Raichle, 1983; Zimmer, 2009). These molecules are unstable and to reach a more

stable form they typically release a positron, a positively charged molecule, which travels a very short distance in the brain until it collides with an electron, which is charged negatively, in a process called annihilation (for more exhaustive reviews see Esser, 2010; or Raichle, 1983). This process releases energy in the form of two gamma rays, two photons of light, which travel in exactly opposite directions. These are detected by coincidence detectors, situated in a ring shape around the subjects's head, which reconstruct the data to locate the origin of the photons (Esser, 2010). Thus, PET allows for the acquisition of images that show the proportional concentration of the radiotracer in the brain (Esser, 2010). Depending on the radiotracer used, it allows for measures of regional Cerebral Blood Flow (rCBF) or Volume (rCFV), oxygen or glucose utilization, as well as the distribution and availability of different receptors or transporters (Carter & Shieh, 2010; Ichise, 2010; Raichle, 1983). However, it has the associated disadvantage of the use of short-lived radiotracers, which require a room-sized machine called cyclotron in order to synthesise these compounds (Carter & Shieh, 2010). A similar technique is the Single Photon Emission Computed Tomography (SPECT) (Bonne, Krausz, & Lerer, 1992; Lewis, 1996). SPECT uses a different type of radiotracers, isotopes which decay with the emission of single photons, and a smaller set of detectors, programmed to detect those single photons, with the associated reduced spatial resolution (Lewis, 1996). Both techniques shared the use of ionizing radiation (Esser, 2010), which limits their frequency of use in a single subject to 4-5 per year. Furthermore, for ethical reasons, these cannot be used in children.

Finally, optical imaging measures such as functional near-infrared spectroscopy (fNIRS) (Jobsis, 1977), use optical fiber detectors placed on the scalp to calculate separately changes in the concentration of oxygenated and deoxygenated blood (Hoshi, 2003).

2.1.4. Advantages of the use of fMRI in ADHD compared to other functional brain imaging methods

The previous sections have reviewed the basic technical concepts of the most commonly used brain functional imaging methods. When selecting the technique to be used in a study, it is necessary to consider its main advantages and disadvantages, and whether it is the most adequate technique to serve for the main aim of the study.

Thus, the use of fMRI to study brain function in ADHD has several strengths when compared to other functional brain imaging techniques. Although its temporal resolution is worse than those from EEG/ERPs or fNIRS, it has a better spatial resolution than these methods (Volkow, Rosen, & Farde, 1997). Furthermore, PET cannot be used in children for ethical reason because it requires the injection of a radioactive substance into the blood stream. In addition, EEG, ERP and fNIRS methods do not allow for the study of subcortical structures, which have shown to have a crucial role in the pathophysiology of the disorder, as it will be reviewed in the next sections of this chapter. It furthermore is non-invasive, as it does not use ionizing radiation like PET. Thus, fMRI is a crucial technique, as it has the best spatial resolution and allows for the study of the function of subcortical structures with a relatively better temporal resolution than PET, the only other technique that allows for that which, as mentioned, cannot be used in children due to the need to inject radioactive substances. MRI is also the only method that allows to study the structure of the brain. The additional advantage is that during an fMRI scan a structural MRI scan can be acquired in relatively short time of 5 minutes, which allows for co-measuring of brain structure.

The limitations of fMRI need to be considered when selecting this technique. Thus, the use of subtraction methods that only permit to obtain measures of relative increases on brain activity is a drawback shared by fMRI, fNIRS and EEG methods. Furthermore, the nature of the relationship between the BOLD signal and brain activity is still not yet well understood. Changes in BOLD signal are thought to reflect neural activity associated with the input and local processing (Lauritzen & Gold, 2003; Logothetis, 2002; Logothetis & Wandell, 2004). However, with increased neural activity, glucose supply has been shown to match neural consumption however, oxygen supply exceeds the needs of that brain region (Fox & Raichle, 1986) and the reason for this mismatch is still not understood (Logothetis & Wandell, 2004). Furthermore, whether neural inhibition results in enhanced or reduced BOLD signal is still under discussion (Arthurs & Boniface, 2002). In addition, the meaning of the negative BOLD signal is not easy to interpret, as it may be due either to active neuronal suppression or to “vascular steal”, which would reflect the reduction in blood flow in a region due to the increase blood flow demand in a neighbouring region (Wade, 2002). As recently reviewed by Logothetis (Logothetis, 2008), fMRI

cannot differentiate between neuromodulation and function-specific activity, and may potentially confuse excitatory and inhibitory responses (Logothetis, 2008).

The main goal of the present study was to observe changes in the different brain networks underlying the performance of ADHD boys in different cognitive tasks after single dose MPH and ATX challenges compared to placebo. Thus, out of those techniques that can be used for research purposes in children, fMRI was selected for this study, given the adequate spatial resolution that would allow for the identification of networks including cortical and subcortical structures underlying the performance of the participants during the different tasks selected.

2.2 Abnormalities in brain structure and structural connectivity in children with ADHD

As reviewed above, the association between behavioural symptoms of ADHD and the presence of structural or functional abnormalities has long been hypothesised (Lange et al., 2010; Taylor, 2011). Similarities between impulsivity and inhibitory problems shown by patients with frontal lobe damage and children with ADHD led to the hypothesis that frontal lobe abnormalities would underlie the inhibitory deficits that, as reviewed in the previous chapter, have been consistently reported in children with ADHD. In the early 90's, the first structural MRI studies conducted in children with ADHD provided the first available evidence of structural brain abnormalities in ADHD patients (Hynd et al., 1993; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990; Hynd et al., 1991).

Gray matter consists on the neuronal and glial cell bodies, arranged as an outer layer covering the surface of the cerebrum, as well as in deep grey matter nuclei (Patestas & Gartner, 2006). White matter consists of cell axons, which may be covered by the myelin sheath, responsible for their white aspect (Patestas & Gartner, 2006). As every organ in our bodies, the integrity of the brain is crucial to preserve its function. The use of structural MRI methods provides information about the integrity of the brain. Thus, regional or general cortical, grey and white matter volumetric differences are presumed to be associated with abnormal neural proliferation and distribution, integrity or myelinisation processes in white matter fibers. Also measures of cortical thickness have been used, defined as the 3-D distance between the two surfaces of the grey matter sheet (from the grey/white matter boundary to the grey/CSF boundary), which represents the number, size, density and arrangements of

cells (neurons, neuroglia and nerves fibers) within the cortical mantle (von Economo, 2009).

It is relevant at this stage to mention the differences between Region of Interest (ROI) and Whole Brain Voxel-Based Morphometric (VBM) methods. The use of ROI methods may be adequate under a number of circumstances such as when there is a strong a-priori hypothesis, as it restricts the analyses conducted to a region of interest hypothesised to be abnormal in a determined pathology (Poldrack, 2007). The limited number of comparisons conducted in ROI analyses increases the statistical power to detect differences between groups however, it does not allow for the identification of abnormalities in other structures that, although not hypothesised a-priori, may be playing a role in the disorder or function studied. On the other hand, VBM methods involve voxel-wise comparisons and therefore do not restrict the analysis to any particular brain region, which allows for a comprehensive study of structures which may be involved in the pathophysiology of the disorder (Ashburner & Friston, 2001). However, given the high number of voxels compared, these methods show decreased statistical power to detect differences, as they have to control for multiple comparisons (Poldrack, Mumford, & Nichols, 2011).

2.2.1. Brain structure abnormalities in children with ADHD

Cross-sectional case-control studies have shown brain structure abnormalities in several regions. Thus, possibly the most consistent abnormalities have been reported in the basal ganglia, where children with ADHD have shown volumetric reductions (Brieber et al., 2007; Carmona et al., 2009; Castellanos et al., 2002; Castellanos et al., 1996; Overmeyer et al., 2001; Qiu et al., 2009; Wang, Jiang, Cao, & Wang, 2007). Furthermore, the relevance of these abnormalities in ADHD is highlighted by the inverse association between the reduced volumes of the ventral striatum in children with ADHD compared to controls and parental ratings of hyperactivity/impulsivity (Carmona et al., 2009), and between the caudate volume and clinician-rated severity of symptoms and with parent-rated attention problems (Castellanos et al., 2002).

These results are compelling and extremely relevant to ADHD, as the evidence has shown the key role of basal ganglia as part of fronto-striatal networks that mediate executive processes (Aron & Poldrack, 2006; Chambers, Garavan, &

Bellgrove, 2009; Rubia, Smith, Taylor, & Brammer, 2007) which, as reviewed in the previous chapter, are impaired in children with ADHD.

In addition, structural abnormalities in the cerebellum have also consistently been reported. Thus, ADHD patients have reduced cerebellar volumes relative to controls (Berquin et al., 1998; Castellanos et al., 2002; Castellanos et al., 1996; Durston et al., 2004; Hill et al., 2003; Mackie et al., 2007), with particularly consistent evidence in the cerebellar vermis where volumetric reduction (Berquin et al., 1998; Bledsoe, Semrud-Clikeman, & Pliszka, 2009; Castellanos et al., 2001; Mackie et al., 2007; McAlonan et al., 2007), reduced area (Bledsoe et al., 2009) and grey matter volumes (Carmona et al., 2005) have been reported. These abnormalities have been associated with the symptomatic presentation of the disorder, as the volume in the vermis of the cerebellum has been negatively associated with severity of ADHD symptoms as assessed by the clinician (Castellanos et al., 2001; Castellanos et al., 2002), and by parent-rated scales (Castellanos et al., 2002). Furthermore, a longitudinal study provided some evidence for the association between the developmental trajectory in the structural abnormalities of the cerebellum and clinical outcome (Mackie et al., 2007). Thus, while all children with ADHD showed persistently reduced cerebellar volumes (Mackie et al., 2007), the developmental trajectory of those patients who exhibited a better clinical outcome (as measured by the Children's Global Assessment Scale –CGAS) paralleled that observed in healthy controls. However, those patients with worse clinical outcomes showed a progressively more pronounced total volumetric difference relative to controls (Mackie et al., 2007).

Abnormalities have been reported not only in specific structures, but also at a more global level. Thus, compared to healthy adolescents, children with ADHD have shown reduced total cerebral brain volume (between 3-8%) (Batty et al., 2010; Carmona et al., 2005; Castellanos et al., 2002; Hill et al., 2003; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Narr et al., 2009; Qiu et al., 2011; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009) as well as reduced total cerebral grey matter (Batty et al., 2010; Brieber et al., 2007; Carmona et al., 2005; Mostofsky et al., 2002; Narr et al., 2009). Furthermore, reduced overall cortical surface and cortical folding has also been reported (Wolosin et al., 2009).

Structural abnormalities have also been reported in frontal regions, including dorsolateral (DLPFC), orbitofrontal (OFC), medial and superior prefrontal regions

(MFC/SFC), where children with ADHD relative to controls have shown volumetric reductions (Hill et al., 2003; Mostofsky et al., 2002; Wang et al., 2007; Wolosin et al., 2009), reduced surface (Sowell et al., 2003), cortical folding (Wolosin et al., 2009), as well as reduced grey matter volumes (Batty et al., 2010; Brieber et al., 2007; Carmona et al., 2005; Castellanos et al., 2002; Durston et al., 2004; McAlonan et al., 2007; Mostofsky et al., 2002; Overmeyer et al., 2001; Plessen et al., 2006; Sasayama et al., 2010). Furthermore, reduced grey matter volumes have also been reported in the cingulate cortex, somatosensory, motor and premotor regions (Carmona et al., 2005; Mostofsky et al., 2002; Overmeyer et al., 2001). Reduced frontal grey matter volumes were negatively associated with severity of symptoms as assessed by the clinician and with parent-rated attention problems (Castellanos et al., 2002), and with inattention symptoms (Brieber et al., 2007), supporting thus the association between structural abnormalities and symptoms of ADHD.

At this point, it is necessary to mention again the relevance of the use of ROI or VBM methods, as only few studies used VBM methods in children with ADHD (Brieber et al., 2007; Carmona et al., 2005; Kobel et al., 2010; McAlonan et al., 2007; Overmeyer et al., 2001; Sasayama et al., 2010; Wang et al., 2007; Yang et al., 2008). ROI analyses restrict the search area, which may bias the results towards selected regions previously hypothesised that will be consistently reported while regions that may be relevant for the disorder but not initially hypothesised may remain unidentified.

Though less frequently studied, volumetric reductions in paediatric ADHD samples have also been reported in other areas involved in emotion processes such as reduced grey matter volume in the parahippocampal gyrus (Carmona et al., 2005), the hippocampus (Brieber et al., 2007) or amygdala (Sasayama et al., 2010), which has also shown reduced surface (Plessen et al., 2006). Furthermore, the morphological abnormalities in the amygdala have been associated with inattention scores (Plessen et al., 2006). Deficits have also been observed in areas that are relevant to attention such as the thalamus (Ivanov et al., 2010), and in temporo-parietal cortices, which have shown reduced volumes (Wang et al., 2007; Wolosin et al., 2009), grey matter volume (Batty et al., 2010; Brieber et al., 2007; Carmona et al., 2005; Kobel et al., 2010; McAlonan et al., 2007; Sasayama et al., 2010) or surface (Wolosin et al., 2009) in children with ADHD compared to healthy controls.

Nevertheless, the abnormalities observed in brain structure in children and adolescents with ADHD are not limited to volumetric reductions, but also increased volumes have been reported in the right inferior prefrontal cortex (IFC) and caudate (Garrett et al., 2008), as well as increased grey matter volumes in the left posterior cingulate cortex (Nakao et al., 2011), bilaterally in parietal regions (Brieber et al., 2007), and right occipital cortex (Wang et al., 2007), as well as increased grey matter density in temporal, parietal and occipital cortices (Sowell et al., 2003). Larger hippocampus has also been reported (Plessen et al., 2006), and morphological abnormalities in the hippocampus have been inversely associated with symptom severity (Plessen et al., 2006).

2.2.2. Meta-analyses on brain structure abnormalities in children with ADHD

Further support to the structural abnormalities observed in children with ADHD is provided by the results from recent meta-analytic studies. A meta-analysis of studies using ROI methods observed reduced volumes in children with ADHD compared to healthy controls in right and total cerebral volumes, posterior inferior cerebellar regions, splenium, right caudate and prefrontal grey matter volumes (Valera, Faraone, Murray, & Seidman, 2007). On the other hand, meta-analytic studies of findings from VBM studies in children with ADHD have shown that the most significant volumetric grey matter reductions are in the right basal ganglia (Ellison-Wright, Ellison-Wright, & Bullmore, 2008; Frodl & Skokauskas, 2012; Nakao et al., 2011). Furthermore, using meta-regression analysis both age and medication status have been associated with these abnormalities, with older patients showing more normal striatal grey matter volumes (Nakao et al., 2011), and those studies with a higher proportion of medicated patients no longer showing striatal grey matter volumetric abnormalities (Frodl & Skokauskas, 2012; Nakao et al., 2011). The normalisation of grey matter volumes in the basal ganglia with age is in line with the first longitudinal imaging study in ADHD that showed normalisation with age of the abnormally reduced caudate volumes in children with ADHD, but not of the other cortical regions that were reduced in gray matter/volume (Castellanos et al., 2002).

Thus, the evidence suggests that ADHD in children most consistently is associated with reduced grey matter volumes in the basal ganglia and cerebellum, which form part of fronto-striatal and fronto-cerebellar cognitive networks underlying diverse executive functions including inhibition, timing, sustained attention and

working memory (Arnsten & Rubia, 2012; Chambers et al., 2009; Rubia, Smith, Taylor, et al., 2007), which, as reviewed in the previous chapter, are typically impaired in children with ADHD. Further mounting evidence supports the presence of reduced regional and grey matter volumes in prefrontal regions. However, given that the majority of the studies used ROI methods, more evidence from VBM studies would be necessary.

2.2.3. Cortical thickness and developmental delay in ADHD

Brain structure abnormalities in ADHD are not restricted to volumetric reductions, but also to reduced cortical thickness, which have been suggested as potential anatomical markers for ADHD (Narr et al., 2009). As defined above, cortical thickness is associated with the size, density and arrangement of the cells within the cortical mantle (von Economo, 2009). Reduced global and regional cortical thinning has been reported, particularly in (but not reduced to) different regions of the prefrontal cortex, anterior temporal regions and lateral and posterior parietal areas (Almeida et al., 2010; Almeida Montes et al., 2012; Batty et al., 2010; Narr et al., 2009; Qiu et al., 2011; Shaw, Eckstrand, et al., 2007; Shaw et al., 2006; Shaw, Sharp, et al., 2009). However, also increased cortical thickness in ADHD patients compared to controls has been reported in posterior temporo-occipital regions, which were positively associated with ADHD criteria (DSM-IV-TR) and whose extent was reduced with age (Almeida Montes et al., 2012).

One of the most significant contributions to our knowledge of structural brain abnormalities in ADHD are the recent longitudinal studies on cortical thickness in ADHD by the group from Shaw (Shaw, Eckstrand, et al., 2007; Shaw et al., 2011; Shaw, Gornick, et al., 2007; Shaw, Lalonde, et al., 2009; Shaw et al., 2006; Shaw et al., 2012; Shaw, Sharp, et al., 2009), which have provided the first direct evidence on the previously hypothesised presence of a developmental delay in ADHD (Rubia, 2007).

Brain maturation processes have been associated with an increase in cortical thickness until the age of 7-8, when it peaks and gives way to cortical thinning, which is thought to be associated with synaptic pruning and increased myelinisation (Shaw, Eckstrand, et al., 2007). This process has shown regional variations, with primary sensory areas attaining their peak of cortical thickness earlier than higher association areas (Shaw, Eckstrand, et al., 2007). Children with ADHD compared to healthy

controls show a developmental delay (up to 4-5 years in prefrontal regions) in the peak of cortical thickness (Shaw, Eckstrand, et al., 2007). However, the developmental trajectory was parallel to that observed in healthy children (Shaw, Eckstrand, et al., 2007). Children with ADHD have shown a developmental delay not only on cortical thickness but also on another index of brain maturation processes, the development of cortical surface area (Shaw et al., 2012). Thus, parallel but delayed trajectories were described across all cortical surfaces, with the more pronounced differences in the right prefrontal and left parietal regions, where they showed a 2-years delay in the mean age of attaining peak surface area (Shaw et al., 2012). Thus, this evidence shows for the first time that ADHD is associated with a delay in the developmental processes in the brain, rather than a deviation from normal developmental trajectories.

In typically developing children, hyperactivity/impulsivity symptoms have been associated with slower cortical thinning rate especially in prefrontal, premotor and temporal regions (Shaw et al., 2011). Furthermore, in healthy developing children under the age of 10, thinner prefrontal (especially right IFC and OFC), cingulate and premotor cortices as well as left temporo-parietal regions were associated with higher scores of attention problems. However, this association disappeared with age, as they showed a slower rate of cortical thinning (Ducharme et al., 2011). Thus, the evidence suggests that children with ADHD show the extreme end of these two dimensions, with reduced cortical thickness and slower rate of cortical thinning, supporting the presence of delay in cortical maturation in ADHD.

Therefore, these studies are highly relevant, as they have provided the first direct evidence of the previously hypothesised maturation delay in the brain of children with ADHD (Rubia, 2007). However, whether patients catch up is unclear, since similar structural abnormalities have been observed in cross-sectional studies in adults with ADHD (for reviews, see Cubillo et al., 2012; as well as Cubillo & Rubia, 2010). Also, if and once the “catch up” has occurred, the efficiency of the network may not be comparable to the one of those who have undergone a typical brain developmental process (Fair et al., 2009). This highlights the need for longitudinal studies that are prolonged well into adulthood to determine the changes in brain structure with age, as well as their association with symptomatic changes in time, whether there are differences in the developmental trajectories of persistent and remitted cases as well as between the different subtypes of the disorder, and how the

presence of comorbid disorders influences the observed developmental delay in ADHD.

In summary, the evidence from MRI studies investigating cortical thickness in ADHD suggests that ADHD is associated with reduced cortical thickness in prefrontal cortices, anterior temporal and posterior parietal regions. These regions showed not only a reduced cortical thickness but also a delay in the time to reach the peak cortical thickness and cortical surface area, which are indexes of brain maturation processes, and associated with cognitive maturation. These studies showing a maturational delay in brain structure development constitute therefore the first evidence for the hypothesis of delayed brain maturation processes in ADHD, a landmark in the field. Furthermore, the reported association in healthy children of both slower cortical thinning rates and thinner prefrontal and temporo-parietal cortices with increased severity of attention problems, hyperactivity and impulsivity symptoms suggests that children with ADHD are at the very end of a spectrum, where the more disturbed these brain maturation processes, the more the severity of the symptoms presented. This is in line with dimensional scales of ADHD symptoms, commonly used in clinical environments, such as the Conner's Parent Rating Scale (CPRS) (Conners, Sitarenios, Parker, & Epstein, 1998) or the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1999). Furthermore, the use of a dimensional adjunct in addition to the categorical diagnosis of ADHD is at present being considered for its inclusion in DSM-V (Swanson, Wigal, & Lakes, 2009).

Thus, the fact that the most pronounced developmental delay was in prefrontal regions followed by temporo-parietal areas, together with the mounting evidence of reduced regional volumes and grey matter volumes in prefrontal and temporo-parietal regions, highlights the relevance of the presence of structural abnormalities in these areas in the disorder.

2.2.4. Abnormalities in structural connectivity in children with ADHD

The different regions in the brain do not work in isolation, but are part of wider neural networks that interact (Castellanos & Proal, 2012), and are connected by white matter fiber tracts (Wakana et al., 2004). Disturbances in white matter are suggestive of altered axonal myelination and/or maturation processes. Not only the disruption of a component of the network may be greatly impairing, but also disruptions in the connections between the different components may alter its

functioning. The development of Diffusion Tensor Imaging (DTI) techniques (defined in section 2.1.1.) allows for the investigation of the disrupted integrity in specific white matter fiber tracts. Thus, there is evidence supporting that the structural abnormalities observed in ADHD patients are not restricted to localized regions but affect inter-regional structural connectivity.

The corpus callosum is the largest fiber tract and the main connector of the two hemispheres of the brain, and plays a key role in not only in facilitating the integration of information from the two hemispheres (Aboitiz, Ide, & Olivares, 2003) but also during attention processes (Banich, 2003). Abnormalities in the corpus callosum have consistently been reported in children with ADHD, who compared to controls have shown global and regional reduced volumes (Hill et al., 2003; McAlonan et al., 2007), areas (Cao et al., 2010; Schnoebelen, Semrud-Clikeman, & Pliszka, 2010), as well as reduced callosal thickness (Luders et al., 2009), with the most consistent findings supporting a volumetric reduction in the splenium of the corpus callosum, as shown by a meta-analytic study (Hutchinson, Mathias, & Banich, 2008). The splenium of the corpus callosum projects to primary sensory regions, posterior parietal and occipital areas, allowing for the interhemispheric connection of homologous regions of the two cerebral hemispheres (Hofer & Frahm, 2006). Furthermore, abnormal developmental trajectories have also recently been reported, with an increased growth rate described in children with ADHD relative to that of healthy controls, which was significant in the anterior corpus callosum, connecting homologous prefrontal fibers, and has been hypothesised as being potentially associated with the abnormalities (structural and functional) observed in prefrontal regions (Gilliam et al., 2011).

Although less consistently, white matter abnormalities have also been described in other brain regions. Thus, reduced white matter volumes have also been reported in bilateral prefrontal, temporal and parietal lobes (Castellanos et al., 2002; Durston et al., 2004; McAlonan et al., 2007; Mostofsky et al., 2002; Overmeyer et al., 2001). However, there are also inconsistent results, with studies where either no differences (Batty et al., 2010; Carmona et al., 2005) or an increased global white matter volume (Narr et al., 2009) have been reported.

DTI studies have furthermore shown disrupted structural connectivity in youths with ADHD in multiple white matter tracts, most consistently in those connecting key fronto-striatal and fronto-parietal projections such as the anterior

corona radiata (connecting the anterior cingulate cortex to the striatum and prefrontal regions), and the right superior longitudinal fasciculus (SLF, connecting posterior temporo-parietal regions to medial prefrontal cortical areas) (for reviews, see Konrad & Eickhoff, 2010; Liston, Malter Cohen, Teslovich, Levenson, & Casey, 2011; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). This was confirmed by a recent meta-analytic study, where reduced white matter integrity was observed in patients with ADHD compared to controls in the right anterior corona radiata, left cerebellar white matter, the internal capsule and the forceps minor (projections from the genu of the corpus callosum to OFC)(van Ewijk et al., 2012). Finally, there is also some evidence for disrupted integrity in the cerebellar peduncles, white matter tracts connecting the cerebellum to cortical and subcortical structures (Bechtel et al., 2009; Kobel et al., 2010; Nagel et al., 2011).

In conclusion, findings from DTI studies show that not only isolated brain regions are impaired in ADHD, but also the inter-regional connections between brain structures that have consistently shown volumetric, white matter, grey matter or cortical thickness reductions in sMRI, most prominently white matter tracts of the corpus callosum, and those comprising fronto-striatal and fronto-parietal projections.

2.2.5. Conclusions on brain structure abnormalities in children with ADHD

Structural MRI studies have provided consistent evidence not only on structural abnormalities in ADHD relative to healthy controls in isolated brain regions, but also in white matter fibers that connect these regions. There is mounting evidence about the presence of volumetric reductions and grey matter abnormalities in the basal ganglia and cerebellum, as well as in the splenium of the corpus callosum and in white matter fiber tracts connecting fronto-parietal and fronto-subcortical regions (for reviews, see Konrad & Eickhoff, 2010; Liston et al., 2011; van Ewijk et al., 2012).

The findings from recent meta-analytic studies on structural MRI are conclusive, and consistently report volumetric grey matter reduction in the right basal ganglia (Ellison-Wright et al., 2008; Frodl & Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007). This is highly relevant, as the basal ganglia together with their connections to frontal and other regions have been shown to be crucial for different executive functions (including temporal processing, attention, inhibition or motivation) in which children with ADHD are impaired (Nigg et al., 2005; Rubia,

Smith, et al., 2007a; Rubia, Halari, Christakou, et al., 2009; Willcutt et al., 2005)(for review see (Rubia, 2011)). Furthermore, an association between the abnormalities in the basal ganglia and symptom severity has been documented (Castellanos et al., 2002). Both meta-regression analyses with age and mixed cross-sectional/longitudinal studies have in addition provided evidence for the normalisation of these deficits with age (Castellanos et al., 2002; Frodl & Skokauskas, 2012; Nakao et al., 2011).

Another key region where the evidence for structural abnormalities in ADHD is compelling is the cerebellum, in particular (but not only) with regards to reduced volumes in the cerebellar vermis (Berquin et al., 1998; Bledsoe et al., 2009; Carmona et al., 2005; Castellanos et al., 2001; Mackie et al., 2007; McAlonan et al., 2007), which has been associated with symptoms of the disorder (Castellanos et al., 2001; Castellanos et al., 2002) and clinical outcome (Mackie et al., 2007). Furthermore, although less numerous, there is also evidence not only of reduced volume of the cerebellum but also of structural reduced integrity of the cerebellar peduncles, which are white matter fibers connecting the cerebellum with cortical and subcortical structures (Bechtel et al., 2009; Nagel et al., 2011). This is especially relevant as the cerebellum is involved not only in motor control but also in other higher cognitive functions in which children with ADHD consistently show deficits, such as in higher-level executive functions (including inhibitory processes or sustained attention) (Arnsten & Rubia, 2012; Steinlin, 2007; Stoodley & Schmahmann, 2009), as well as in temporal processing (Aso, Hanakawa, Aso, & Fukuyama, 2010; Rubia & Smith, 2004; Wiener, Turkeltaub, & Coslett, 2010).

The evidence is also mounting for the presence of reduced regional volumes and grey matter volumes in prefrontal regions and, although less numerous, also in temporo-parietal regions. This evidence, together with the recent findings of reduced cortical thickness and a developmental delay in brain maturation processes in ADHD, which are particularly pronounced in prefrontal and temporo-parietal cortices, highlight the relevance of the structural abnormalities in these regions in the disorder. Interestingly, recent studies have linked the presence of inattention and hyperactivity symptoms to the developmental trajectories of cortical thickness in prefrontal and temporo-parietal regions in healthy children (Ducharme et al., 2011; Shaw et al., 2011). Thus, these studies suggest that children with ADHD may show the extreme expression of the attention problems and hyperactive/impulsive dimensions, as they have consistently shown reduced cortical thickness and slowed (delayed) cortical

thinning rate (Almeida et al., 2010; Almeida Montes et al., 2012; Narr et al., 2009; Shaw, Eckstrand, et al., 2007; Shaw, Lalonde, et al., 2009; Shaw et al., 2006; Shaw, Sharp, et al., 2009).

However, although this constitutes an extremely relevant evidence, longer-term longitudinal studies prolonged well into adulthood are needed in order to identify age-related changes in brain structure, their association with symptomatic improvement, differences in developmental brain maturation processes between persistent and remitted cases or between ADHD subtypes, as well as the influence of comorbid diagnoses on such developmental delay in ADHD.

The evidence from studies on structural abnormalities in children with ADHD suggests that ADHD is characterised not only by disrupted isolated components of brain networks, but also by altered connections between their different components. Thus, the evidence is highly consistent with regards to the presence of reduced inter-regional structural connectivity, in particular in the splenium of the corpus callosum and in white matter fiber tracts connecting fronto-parietal and fronto-subcortical areas (for reviews, see Konrad & Eickhoff, 2010; Liston et al., 2011; van Ewijk et al., 2012).

An important aspect to consider when reviewing the evidence on brain structural abnormalities in ADHD is the use of ROI or VBM methods. This is highly relevant, as ROI analyses increase the power to detect differences between groups but limit the search area, and may therefore bias the results as only certain regions previously hypothesised will be consistently reported while regions that may be relevant for the disorder but not initially hypothesised may remain unidentified. Two recent meta-analysis (Frodin & Skokauskas, 2012; Nakao et al., 2011) have shown that out of the wealth of studies conducted, very few had used VBM methods in children with ADHD (Brieber et al., 2007; Carmona et al., 2005; Kobel et al., 2010; McAlonan et al., 2007; Overmeyer et al., 2001; Sasayama et al., 2010; Wang et al., 2007; Yang et al., 2008).

A second area where question marks are still present is the relationship and interdependence between the reported abnormalities in white and grey matter. From the available evidence, it cannot be concluded whether grey matter abnormalities (cortical thickness, volume, area, surface, density) influence (or how they do it) the structure, volume or integrity of white matter tracts, or viceversa. As mentioned above, only longitudinal studies with large samples that follow up subjects into adulthood and study the developmental trajectories of grey and white matter, as well

as their association with symptoms and cognitive function would provide some light on this question.

Despite the relative consistency of the structural abnormalities reported, their functional significance still needs to be elucidated. We can only hypothesise about their role in the disorder, as these structural abnormalities have not yet shown to be specific to ADHD, and do not necessarily lead to ADHD symptoms. Despite its relevance, only some authors have investigated the association between the reported structural abnormalities and ADHD symptoms. Some studies have shown an association between inattention or hyperactivity symptoms and reduced grey matter volumes in frontal and temporal cortices, caudate and cerebellum (Castellanos et al., 2002), with grey matter volumetric reduction in the left MFC (which was not significantly reduced in ADHD patients) (Brieber et al., 2007), reduced volume of right ventral striatum (VS) (Carmona et al., 2009), surface alterations in the amygdala (Plessen et al., 2006) and thalamus (Ivanov et al., 2010), reduced grey matter density in occipital regions (Sowell et al., 2003) and reduced cortical thickness in frontal (Almeida et al., 2010; Almeida Montes et al., 2012) and parietal regions (Almeida Montes et al., 2012). However, there are also studies where no association has been reported between symptoms and structural abnormalities, such as with the reduced cortical thickness reported by Narr et al (Narr et al., 2009) or with the abnormal volume in the cerebellum reported by Berquin et al (Berquin et al., 1998).

Also, how these structural abnormalities relate to impaired cognitive function still need to be elucidated, as very few of the studies have tried to establish that connection, unfortunately without conclusive results. Thus, performance during a GNG task has shown no association between the reduced grey matter volumes or thinner IFC observed in ADHD patients relative to controls (Batty et al., 2010), but a positive association with the circumference of the corpus callosum was observed (that did not differ between children with ADHD and healthy controls) (McNally et al., 2010). Furthermore, in children with ADHD, better inhibitory function was associated with greater grey matter volumes in the anterior cingulate (ACC), right lentiform nucleus and medial temporal lobe (McAlonan et al., 2009), whereas response shifting was associated with greater grey matter volumes in the right basal ganglia and cerebellum (McAlonan et al., 2009). However, it is necessary to note here that only volumetric reductions were observed in the basal ganglia, whereas the cerebellum, temporal regions and ACC did not show volumetric differences in grey matter

between healthy children and those with ADHD (McAlonan et al., 2007). Finally, during a CPT task, within children with ADHD (but not within the control group), worse performance was associated with larger SFC volumes (reduced in ADHD children compared to healthy controls) (Hill et al., 2003). Thus, there is very limited evidence about the association between the reported structural abnormalities and impaired cognitive functioning in ADHD.

Nevertheless, it is important to highlight the small sample sizes of most of the studies, which significantly limits the statistical power to detect significant differences or associations with behaviour or cognitive performance. Additionally, the inclusion of subjects with different ADHD diagnostic subtypes (Carmona et al., 2005; Durston et al., 2004; Garrett et al., 2008; Mackie et al., 2007; Mostofsky et al., 2002; Qiu et al., 2009; Wolosin et al., 2009), comorbid conditions (Almeida et al., 2010; Batty et al., 2010; Carmona et al., 2005; Durston et al., 2004; Garrett et al., 2008; Hill et al., 2003; Mackie et al., 2007; McAlonan et al., 2007; McAlonan et al., 2009; Mostofsky et al., 2002; Overmeyer et al., 2001; Plessen et al., 2006; Qiu et al., 2009; Wolosin et al., 2009), previously medicated (Brieber et al., 2007; Carmona et al., 2009; Castellanos et al., 2001; Durston et al., 2004; Garrett et al., 2008; Hill et al., 2003; Mackie et al., 2007; McAlonan et al., 2007; McAlonan et al., 2009; Mostofsky et al., 2002; Narr et al., 2009; Overmeyer et al., 2001; Plessen et al., 2006; Qiu et al., 2009; Sowell et al., 2003) and mixed genders (Almeida et al., 2010; Batty et al., 2010; Carmona et al., 2009; Carmona et al., 2005; Garrett et al., 2008; Hill et al., 2003; Narr et al., 2009; Overmeyer et al., 2001; Plessen et al., 2006; Qiu et al., 2009; Sowell et al., 2003; Wolosin et al., 2009) increases the heterogeneity of the samples and therefore decreases the ability of the studies to detect differences or to replicate previous results.

A potential caveat of the reviewed studies is the inclusion of subjects with comorbid conditions, most commonly the frequent diagnosis of CD/ODD, as their contribution to the structural abnormalities cannot be easily disentangled. Those studies that have tried to identify the impact of those comorbid conditions on the findings showed inconsistent results. Some studies have reported a lack of effect of the presence of comorbid ODD/CD on the reduced volumes, surfaces, cortical folding index or cortical thickness of the corpus callosum observed in ADHD children compared to controls (Luders et al., 2009; Plessen et al., 2006; Wolosin et al., 2009). However, others have reported an increased effect of the abnormalities in children

with ADHD when they presented with comorbid CD/ODD, as the more pronounced volumetric reductions in globus pallidus and cerebellum shown by children with ADHD and comorbid ODD/CD compared to those children without comorbid conditions (McAlonan et al., 2007). The opposite has also been reported, with more pronounced structural abnormalities when comorbid cases are accounted for. Thus, children with pure ADHD showed smaller caudate volumes than those with comorbid CD (Hill et al., 2003), or more marked reductions of grey matter volumes in temporo-occipital regions and amygdala (Sasayama et al., 2010). Therefore, preferably non-comorbid samples should be studied in order to avoid this confound.

Finally, as with neuropsychological studies, the inclusion of different subtypes of the disorder in some of the studies may have increased the heterogeneity of the already small samples. It seems necessary to study each of the different subtypes separately, or at least to include sample sizes that are large enough to allow for comparisons between the different subtypes.

Therefore, studies including large samples with longitudinal measures of cognitive function, brain structure, fMRI measures, structural and functional connectivity measures and symptomatic changes that allow for the study of the association between abnormalities on brain structure/connectivity and symptoms and/or cognitive functions are still needed. These studies would shed light not only on the presence of abnormalities in grey and white matter and structural connectivity in the brain of children with ADHD but also on their progress in time, their association with symptoms and cognitive functions, and the differences and similarities between subtypes.

2.3 ADHD and fMRI studies

The description of the cognitive deficits in EF in children with ADHD suggested the presence of abnormalities in frontal brain regions, given the similarities between these deficits and those observed in patients with frontal lobe damage (Mattes, 1980). FMRI studies have in fact confirmed the view that fronto-striatal networks in the context of inhibitory control functions are underfunctioning in children with ADHD. However, abnormalities have been reported not only during inhibitory tasks in fronto-striatal regions but also in more wide-spread fronto-striato-parietal and fronto-cerebellar networks during tasks involving other cognitive processes such as sustained attention, temporal processing, working memory, reward

and motivation related processes (Castellanos & Proal, 2012; Cubillo et al., 2012; Cubillo & Rubia, 2010; Durston, van Belle, & de Zeeuw, 2010; Makris et al., 2009; Rubia, 2011)). This evidence is reviewed below.

2.3.1 Deficits during inhibitory processes

2.3.1.1. Motor inhibition

During motor response inhibition tasks like the GNG and SST tasks (described in the previous chapter), healthy adults and adolescents show activation in a network comprising predominantly right IFC and right DLPFC, supplementary motor area (SMA), ACC, caudate, thalamus and inferior parietal regions (Chambers et al., 2009; Rubia, Russell, et al., 2001; Rubia, Smith, Brammer, & Taylor, 2003; Rubia, Smith, Taylor, et al., 2007; Rubia et al., 2006). Especially relevant is the right IFC, a key inhibitory region underlying motor inhibition processes (Aron et al., 2007; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron & Poldrack, 2006; Aron, Robbins, & Poldrack, 2004; Chambers et al., 2006; Chambers et al., 2009; Chevrier, Noseworthy, & Schachar, 2007; Goghari & MacDonald, 2009; Ridderinkhof, van den Wildenberg, S.J., & Carter, 2004; Rubia, Smith, et al., 2003; Rubia, Smith, Taylor, et al., 2007; Rubia et al., 2006) as well as the caudate (Chambers et al., 2009; Chevrier et al., 2007; Li, Yan, Sinha, & Lee, 2008). The ACC is involved in performance and conflict monitoring processes (Botvinick, Cohen, & Carter, 2004; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), while the SMA and pre-SMA are involved in motor inhibition as well as motor execution processes such as response selection, attention to action and attention to intention (Lau, Rogers, Ramnani, & Passingham, 2004; Lau, Rogers, Haggard, & Passingham, 2004; Mostofsky & Simmonds, 2008; Sharp et al., 2010; Simmonds, Pekar, & Mostofsky, 2008; Tabu, Mima, Aso, Takahashi, & Fukuyama, 2011).

Children with ADHD have consistently shown underactivation in these key fronto-striatal areas when compared to healthy participants during motor response inhibition paradigms. Thus, reduced activation has been reported during successful inhibitory trials in the SST and GNG tasks in right and left IFC (Booth et al., 2005; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Epstein et al., 2007; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011; Rubia, Cubillo, et al., 2010; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia, Smith, Brammer, Toone, &

Taylor, 2005), DLPFC and MFC (Booth et al., 2005; Durston et al., 2006; Epstein et al., 2007; Mulder et al., 2008; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004); ACC/SMA (Durston et al., 2006; Epstein et al., 2007; Mulder et al., 2008; Rubia, Halari, Mohammad, et al., 2011; Rubia, Cubillo, et al., 2010; Rubia, Overmeyer, et al., 1999; Smith, Taylor, Brammer, Toone, & Rubia, 2006; Suskauer et al., 2008; Tamm et al., 2004) and striatum (most prominently, in the caudate nucleus)(Booth et al., 2005; Durston et al., 2003; Epstein et al., 2007; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005; Suskauer et al., 2008)((Cubillo et al., 2012; for a meta-analysis, see Dickstein, Bannon, Castellanos, & Milham, 2006; Durston et al., 2010; for reviews, see Rubia, 2011).

During unsuccessful inhibition in the tracking SST reduced activation has been reported in children with ADHD compared to healthy controls in right and left MFC and IFC (Rubia, Halari, Mohammad, et al., 2011; Rubia, Cubillo, et al., 2010) and ACC (Pliszka, Glahn, et al., 2006; Rubia, Cubillo, et al., 2010). Furthermore, the underactivation observed in right IFC/MFC during unsuccessful inhibition, and in left DLPFC during successful inhibition in the SST, were disorder-specific when compared to children with obsessive compulsive disorder (OCD) and CD, respectively ((Rubia, Cubillo, et al., 2010; Rubia et al., 2008), for a review see (Rubia, 2011)).

Dysfunctions in other regions have been less consistently reported. The Stop stimuli are highly salient during the task and therefore, in addition to inhibitory areas, regions involved in visuo-spatial attention allocation to salient stimuli including the posterior cingulate cortex (PCC), precuneus or temporo-parietal regions (Arnsten & Rubia, 2012; Cavanna & Trimble, 2006; Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001; Mohanty, Gitelman, Small, & Mesulam, 2008; Sack, 2009; Steinlin, 2007) are also activated. Children with ADHD compared to healthy controls have shown reduced activation during both successful and unsuccessful inhibition in bilateral thalamus (Booth et al., 2005; Rubia, Halari, Mohammad, et al., 2011). Furthermore, underactivation has been observed during successful inhibition trials in GNG and SST tasks in the temporo-parietal junction (Booth et al., 2005; for a meta-analysis, see Dickstein et al., 2006; Durston et al., 2006; Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Rubia et al., 2005; Schulz et al., 2004; Suskauer et al., 2008), cerebellum (Rubia, Halari, Mohammad, et al., 2011; Schulz et al., 2004; Suskauer et al., 2008), and in precuneus and PCC both during failed and successful

inhibitory trials (Rubia, Halari, Mohammad, et al., 2011; Rubia et al., 2008; Rubia et al., 2005).

The abnormalities observed in ADHD are not restricted to reduced activation, but also increased activation has been reported. This has been traditionally interpreted either as a compensatory recruitment to perform the tasks, or as enhanced activation that interferes with the recruitment of key areas for the performance of the task. Thus, a meta-analytic study showed increased activation in children with ADHD compared to healthy control subjects during response inhibition tasks in the left MFC and in the right paracentral gyrus (Dickstein et al., 2006). During Stop tasks, enhanced activation in children with ADHD compared to healthy controls has been reported during successful inhibition in left superior temporal gyrus (STG) (Rubia et al., 2008). During GNG tasks, increased activation was observed in IFC and MFC regions, ACC/PCC, temporo-parietal and occipital cortices (Durstun et al., 2003; Schulz et al., 2004; Tamm et al., 2004).

Whereas Tamm et al (Tamm et al., 2004) highlight the potential compensatory role of the enhanced activation observed in temporal regions, it is noteworthy the special characteristics of the samples in the other studies. Schulz et al (Schulz et al., 2004) included subjects who were older than other samples (mean age was 18 years) and who had had a long history of stimulant medication. Furthermore, 50% of the sample did not fulfil criteria for a full diagnosis of ADHD at the time of the study (Schulz et al., 2004). In the case of Durston et al (Durstun et al., 2003), the relatively young age of the subjects needs to be considered when compared to other studies (children are 6-10 years old).

FMRI studies that have used these paradigms have observed not only brain activation differences between groups but also performance differences, which is remarkable given the small number of participants (with the accompanying loss of power to detect between-group differences) typically included in fMRI studies as compared to those included in neuropsychological studies. However, there is some debate about how to interpret performance differences between groups in functional imaging studies. If performance of the two groups in the task differs, brain activation differences must be interpreted with caution, as there may be other factors associated with those performance differences that can account for the reported brain activation differences rather than the diagnosis (Church, Petersen, & Schlaggar, 2010). The other side of the argument is also possible: when the clinical group does not differ from the

control group and differences on brain activation are observed, then the question arises on what does it mean? There are a number of options to address these performance differences. One of them is to use paradigms where patients have consistently shown deficits in neuropsychological studies, and to adjust them for their use in fMRI studies in order to ensure everyone performs at its best level, such as in the individually tracked version of the SST (Rubia, Smith, et al., 2003). Another option is to investigate the association between performance and brain activation differences. However, and potentially due to the small sample sizes of the majority of the studies reviewed, the evidence for such association in ADHD is reduced.

Thus, activation differences in the left DLPFC were associated with the main inhibitory index (SSRT) in healthy controls, but not in the ADHD group (Rubia et al., 2008). Epstein et al (Epstein et al., 2007) showed that activation in right IFC, which was reduced in patients compared to controls, was associated both in ADHD patients and controls (separately) with better discrimination (d-prime, index of perceptual sensitivity to targets) in the inhibitory task (Epstein et al., 2007). Activation in frontopolar and cingulate regions (where patients showed enhanced activation compared to healthy controls) was positively associated with commission errors (increased in patients compared to controls) only within the healthy control group but not within patients (Schulz et al., 2004). Finally, in ADHD boys, post-error go reaction times were positively associated with activation in left IFC, premotor, dorsal MFC and thalamic regions, which were underactivated in patients when compared to healthy control boys (Rubia, Halari, Mohammad, et al., 2011).

Some of the studies have also tested for the potential association between ADHD symptoms and areas of observed dysfunction. Hyperactivity symptoms as measured by the Strengths and Difficulties Questionnaire (SDQ) have been associated with the underactivation observed in patients compared to controls in the key inhibitory function, the right IFC (Rubia et al., 2005) and in the PCC/precuneus (Rubia et al., 2005). There are also some studies where this association has been tested and no significant results have been reported (Rubia, Cubillo, et al., 2010; Schulz et al., 2004).

To sum up, the evidence from studies using motor response inhibition tasks suggests that children with ADHD show underactivation in key regions for this process, most consistently in the bilateral IFC and the caudate.

2.3.1.2. Interference inhibition

During interference inhibition tasks, healthy subjects show activation in a predominantly (but not exclusively) left lateralised network (Nee, Wager, & Jonides, 2007) including IFC and DLPFC, ACC, basal ganglia and left parietal regions (Cabeza & Nyberg, 2000; Christakou et al., 2009; Derrfuss, Brass, Neumann, & von Cramon, 2005; Laird et al., 2005; Liu, Banich, Jacobson, & Tanabe, 2004; Rubia et al., 2006).

The left IFC has shown to be crucial for interference inhibition and response selection (Chikazoe et al., 2009; Dodds, Morein-Zamir, & Robbins, 2011; Goghari & MacDonald, 2009), the ACC is key for performance monitoring and conflict detection processes (Botvinick et al., 2004; Braver, Barch, Gray, Molfese, & Snyder, 2001; Rushworth, Walton, Kennerley, & Bannerman, 2004) whereas the striatum, in particular the putamen has been involved in stimulus-response learning patterns (Grahn, Parkinson, & Owen, 2008).

Interference inhibition tasks typically load also on selective attention processes, as the subjects have to selectively focus their attention on the relevant aspects of the target stimuli in the task so as to perform correctly. Thus, activation is typically also observed in the temporo-parietal junction and PCC, areas engaged in selective attention (Corbetta & Shulman, 2002; Mesulam et al., 2001; Mohanty et al., 2008; Sack, 2009; Small et al., 2003).

During conflict/interference inhibition conditions in Simon tasks (Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2011) and similar interference inhibition tasks (Konrad et al., 2006; Vaidya, Bunge, Dudukovic, & Zalecki, 2005; Vloet et al., 2010), children with ADHD compared to healthy peers have shown reduced activation in right and left IFC (Rubia, Halari, Cubillo, et al., 2011; Vaidya et al., 2005), basal ganglia (mostly putamen) (Konrad et al., 2006; Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2011; Vloet et al., 2010), in SMA/ACC (Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2011), PCC (Rubia, Halari, Cubillo, et al., 2011), temporal cortices (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Smith, et al., 2009), precuneus (Rubia, Halari, Smith, et al., 2009), and right parietal lobe (Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2011). Furthermore, a discriminant analysis showed that activation patterns in the right inferior parietal lobe (IPL), which showed disorder-specific underactivation in children with ADHD compared to children with OCD, correctly classified ADHD

patients with 90% sensitivity (Rubia, Cubillo, et al., 2011). In addition, not only reduced activation in isolated brain regions has been reported, but also reduced functional connectivity between IFC and superior parietal lobe during interference inhibition (Vloet et al., 2010), which supports the presence of dysfunctional fronto-parietal interference inhibition networks.

However, there are also studies where either no between group differences in brain activation (Smith, Taylor, et al., 2006) or increased activation was detected in the group of patients compared to controls during these paradigms (Konrad et al., 2006; Schulz et al., 2005). Increased and presumably compensatory activation was observed in patients compared to typically developing children in left superior parietal lobe (Konrad et al., 2006). During a stimulus-response interference inhibition task, increased activation was observed in left IFC (ventrally located) (Schulz et al., 2005). In a more cognitively demanding integrated task with both stimulus-response interference and response competition interference, enhanced activation in children with ADHD compared to controls was observed in the left ACC, anterior right MFC, right IFC and left basal ganglia (caudate and globus pallidus) (Schulz et al., 2005). However, it is necessary to consider once more the special characteristics of the sample to interpret the results correctly, since 50% of the participants did not fulfil criteria for a full diagnosis of ADHD at the time of the study, had a long-term medication history and were older than other samples studied (Schulz et al., 2005).

Despite the presence of performance differences between children with ADHD and controls in some of the studies (Rubia, Halari, Smith, et al., 2009; Smith, Taylor, et al., 2006) (Konrad et al., 2006; Rubia, Halari, Cubillo, et al., 2011; Vaidya et al., 2005; Vloet et al., 2010), only few have reported an association between differences in brain activation and performance in the task. Thus, a regression analysis showed that better interference suppression in ADHD was positively associated with BOLD response in left IFC, insula, caudate, thalamus and temporo-parietal regions (Vaidya et al., 2005), and conflict error was negatively associated with activation in PCC and precuneus (underactivated in ADHD patients relative to controls) in the control group but not in the ADHD group (Rubia, Halari, Smith, et al., 2009). Furthermore, the underactivation shown by children with ADHD relative to controls in basal ganglia was associated with ADHD symptom severity (Konrad et al., 2006; Rubia, Halari, Cubillo, et al., 2011). Other studies, however, have shown no association between differences in BOLD response and ADHD symptoms (Rubia, Cubillo, et al., 2011;

Rubia, Halari, Smith, et al., 2009; Vaidya et al., 2005), potentially due to small sample sizes.

The reviewed evidence suggests therefore that children with ADHD during interference inhibition tasks show underactivation in key areas for conflict detection, stimulus-response learning and selective attention, necessary for the correct performance of the task, most prominently in the ACC, putamen and temporo-parietal regions.

2.3.1.3. Cognitive flexibility

During cognitive flexibility tasks healthy subjects typically show activation in bilateral DLPFC and IFC, ACC and IPL (Buchsbaum, Greer, Chang, & Berman, 2005; Derrfuss et al., 2005; Rubia et al., 2006; Smith, Taylor, Brammer, & Rubia, 2004) (for a meta-analysis, see Wager, Jonides, & Reading, 2004). The DLPFC has been associated with the monitoring of task-relevant information (Luks, Simpson, Dale, & Hough, 2007) and the selection of an alternative response (Badre & Wagner, 2004). Furthermore, the medial basal ganglia have shown a relevant role in flexibility of responding processes (Grahn et al., 2008). Attention shifting has been associated with the IPL, in particular the region close to the intraparietal sulcus (Dodds et al., 2011; Wager et al., 2004).

At the brain activation level, reduced activation during cognitive flexibility tasks has been reported in children with ADHD relative to controls bilaterally in key regions including bilateral IFC (Rubia, Hyde, et al., 2010; Rubia, Halari, et al., 2010; Smith, Taylor, et al., 2006), left DLPFC (Rubia, Halari, et al., 2010), basal ganglia (Rubia, Cubillo, et al., 2010), (Smith, Taylor, et al., 2006), ACC and PCC (Rubia, Hyde, et al., 2010; Rubia, Cubillo, et al., 2010; Rubia, Halari, et al., 2010), and temporo-parietal regions (Rubia, Hyde, et al., 2010; Rubia, Halari, et al., 2010; Smith, Taylor, et al., 2006). It was furthermore observed that when patterns of brain activation in children with ADHD are compared to those observed in children with other paediatric psychiatric disorders, the underactivation observed in IFC, left basal ganglia, ACC and PCC and parietal cortex was specific to ADHD and not shared by paediatric OCD patients (Rubia, Cubillo, et al., 2010). Furthermore, the pattern of reduced activation in bilateral IFC and left DLPFC was also disorder-specific when compared to children with CD (Rubia, Halari, et al., 2010).

Only one fMRI study has reported differences at a performance level during a cognitive flexibility paradigm, with children with ADHD compared to healthy peers showing slower reaction times to repeat trials and greater within-subject variability during repeat trials (Smith, Taylor, et al., 2006). However, no association between these performance differences (or symptoms) and brain activation has been observed.

It can hence be concluded from the available evidence that children with ADHD show underactivation relative to controls in typical areas that mediate cognitive flexibility, in bilateral IFC, caudate and putamen, ACC/PCC and parietal regions during cognitive flexibility tasks.

2.3.1.4. Summary of findings from inhibitory tasks

A number of factors need to be considered when interpreting the findings from the reviewed studies, such as the small sample sizes (Booth et al., 2005; Durston et al., 2006; Durston et al., 2003; Epstein et al., 2007; Mulder et al., 2008; Schulz et al., 2005; Tamm et al., 2004; Vaidya et al., 2005; Vloet et al., 2010), which in most of the cases are below the suggested number of 20 participants in each group (Thirion et al., 2007). Furthermore, the frequent inclusion of comorbid disorders (Durston et al., 2006; Durston et al., 2003; Epstein et al., 2007; Konrad et al., 2006; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Suskauer et al., 2008), different subtypes of ADHD (Booth et al., 2005; Durston et al., 2003; Epstein et al., 2007; Konrad et al., 2006; Mulder et al., 2008; Schulz, Bedard, Czarnecki, & Fan, 2011; Schulz et al., 2005; Suskauer et al., 2008; Vloet et al., 2010), or males and females within the same sample (Booth et al., 2005; Durston et al., 2003; Epstein et al., 2007; Pliszka, Glahn, et al., 2006; Suskauer et al., 2008; Vaidya et al., 2005) increase the heterogeneity of the samples and complicates the interpretation of the findings, especially in studies with such small sample sizes. However, possibly the most important confound is the inclusion of subjects with a previous history of stimulant medication (Booth et al., 2005; Durston et al., 2006; Durston et al., 2003; Epstein et al., 2007; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Schulz et al., 2005; Suskauer et al., 2008; Tamm et al., 2004; Vaidya et al., 2005), given the long-term effects of stimulant medication administration on brain structure and function (Frodl & Skokauskas, 2012; Konrad, Neufang, Fink, & Herpertz-Dahlmann, 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009). Finally, we also need to take into account the frequent use of ROI analysis (Durston et al., 2006; Epstein et al., 2007; Mulder et al., 2008; Pliszka, Glahn, et al.,

2006; Schulz et al., 2004; Suskauer et al., 2008), that restricts the areas to study and increases the statistical power to detect differences in these regions, although at the expense of leaving aside other regions that may be playing a role in the disorder (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). Therefore, the use of ROI analyses over whole brain methods may bias the results as only some areas are studied, and therefore may increase the consistency of the findings with regards to the dysfunctions observed on brain areas, while other regions that may be relevant for the disorder are left aside and although may be dysfunctional, these will remain undetected.

However, and despite these limitations, the evidence is relatively consistent with regards to abnormalities in children and adolescents with ADHD during inhibitory tasks, as brain imaging studies have most consistently shown reduced activation in bilateral IFC, and caudate during motor response inhibition (Mulder et al., 2008; Rubia, Halari, Mohammad, et al., 2011; Rubia, Cubillo, et al., 2010; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005), in ACC and temporo-parietal regions during interference inhibition (Konrad et al., 2006; Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Smith, et al., 2009) and in bilateral IFC, putamen and caudate, ACC/PCC and parietal regions during cognitive flexibility (Rubia, Halari, et al., 2010; Smith, Taylor, et al., 2006).

2.3.2 Deficits during attention processes

2.3.2.1 Sustained attention

Healthy subjects during sustained attention tasks such as the CPT activate a predominantly right lateralized network including IFC and DLPFC, pre-SMA, striatum, thalamus, temporal areas, inferior parietal regions and cerebellum (Adler et al., 2001; Cabeza & Nyberg, 2000; Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; Smith, Halari, Giampetro, Brammer, & Rubia, 2011; Tana, Montin, Cerutti, & Bianchi, 2010; Voisin, Bidet-Caulet, Bertrand, & Fonlupt, 2006). The cerebellum as part of the fronto-cerebellar neural circuits is involved in sustained attention processes (Arnsten & Rubia, 2012; Lawrence et al., 2003; Steinlin, 2007; Stoodley & Schmahmann, 2009; Voisin et al., 2006), the pre-SMA is involved in attention to action and response selection (Lau, Rogers, Ramnani, et al., 2004; Mostofsky & Simmonds, 2008; Sharp et al., 2010; Simmonds et al., 2008), and temporo-parietal

regions have shown to be involved in visual-spatial attention control (Corbetta & Shulman, 2002).

Children with ADHD have shown deficits in these areas underlying sustained attention processes. During fMRI adaptations of sustained attention tasks, reduced activation has been reported in ADHD boys compared to healthy controls in dorsolateral, ventrolateral and ventromedial/orbito/inferior prefrontal cortices (Christakou et al., 2012; Rubia, Halari, Cubillo, Mohammad, & Taylor, 2009; Rubia, Smith, et al., 2009), as well as in striatum, thalamus, temporo-parietal regions and cerebellum (Christakou et al., 2012; Rubia, Halari, Cubillo, et al., 2009). However, enhanced potentially compensatory activation has also been described in precuneus, temporo-occipital regions and cerebellum, which was furthermore correlated with the reduced activation in prefrontal areas (Christakou et al., 2012; Rubia, Smith, et al., 2009). In addition, the reduced activation in ventrolateral prefrontal cortex (VLPFC) and increased activation observed in the cerebellum were disorder-specific to children with ADHD when compared to children with CD (Rubia, Smith, et al., 2009). The increased number of omission errors observed in patients compared to healthy controls was associated with activation in VLPFC (across all subjects) (Rubia, Smith, et al., 2009), and with parietal activation within ADHD (Rubia, Halari, Cubillo, et al., 2009). Furthermore, within ADHD patients, the number of premature responses was negatively associated with the enhanced activation observed in the precuneus compared to that of healthy controls (Christakou et al., 2012).

In addition, ADHD patients relative to healthy controls have shown reduced functional connectivity during sustained attention between IFC, basal ganglia, parietal cortices and cerebellum (Rubia, Halari, Cubillo, et al., 2009), which supports the presence of dysfunctions not only on isolated specific brain regions, but in fronto-striato-parieto-cerebellar network underlying sustained attention processes.

Therefore, the evidence suggests the presence of reduced functioning and reduced functional connectivity in children with ADHD compared to controls in regions involved in sustained attention most consistently in lateral prefrontal, striato-thalamic and temporo-parietal regions and cerebellum.

2.3.2.2. Attention allocation

During oddball tasks measuring attention allocation, healthy subjects have shown brain activation in a network involving IFC and DLPFC, insula, ACC and

PCC, as also in IPL and temporo-occipital regions (Ardekani et al., 2002; Clark, Fannon, Lai, Benson, & Bauer, 2000; Downar, Crawley, Mikulis, & Davis, 2002; Rubia, Smith, Taylor, et al., 2007). Activation differences have been reported between children with ADHD and healthy comparison subjects during different oddball tasks. In patients, reduced activation has been observed in IFC/MFC (Rubia, Halari, Smith, et al., 2009), ACC (Konrad et al., 2006), basal ganglia (Konrad et al., 2006; Rubia, Cubillo, et al., 2011; Rubia, Smith, Brammer, & Taylor, 2007b) and thalamus (Rubia, Smith, et al., 2007b; Tamm, Menon, & Reiss, 2006). As mentioned above, underactivation in regions involved in visuo-spatial attention has also been reported during oddball tasks, in particular in PCC (Rubia, Cubillo, et al., 2011; Rubia, Smith, et al., 2007b) and temporo-parietal cortices (Rubia, Smith, et al., 2007b; Stevens, Pearlson, & Kiehl, 2007; Tamm et al., 2006). The underactivation observed in left IFC/MFC, caudate and PCC was disorder specific when compared to children with CD and OCD (Rubia, Cubillo, et al., 2011; Rubia, Halari, Smith, et al., 2009).

Some performance differences have been reported in these studies, although not all the studies have investigated their association with brain activation. Children with ADHD compared to healthy controls have shown an increased intra-subject variability of response to oddball trials (Rubia, Smith, et al., 2007b) which was negatively associated with the BOLD signal in the basal ganglia, thalamus, temporal regions and cerebellum within ADHD patients as shown by a whole brain regression analysis (Rubia, Smith, et al., 2007b). The increased commission errors committed by ADHD children compared to controls was negatively associated with the percentage of voxels activated in parietal regions within controls but not within the ADHD groups (Tamm et al., 2006). Finally, longer reaction time (RT) to target stimuli for ADHD subjects compared to healthy controls has also been reported, but the authors did not investigate their association with BOLD signal changes (Stevens, Pearlson, et al., 2007). Only one study has shown association between symptoms and brain activation, where symptom severity was negatively associated within ADHD patients with intensity of the BOLD signal in PCC, which was underactivated in ADHD boys (Rubia, Cubillo, et al., 2011).

The reviewed evidence therefore suggests underactivation in children with ADHD relative to healthy control children during attention allocation tasks most consistently in the PCC and temporo-parietal cortices, as well as in thalamus and basal ganglia.

2.3.2.3 Summary of findings from attention tasks

It can therefore be concluded that the available evidence supports the presence of dysfunctions in brain networks underlying sustained attention and attention allocation processes, most consistently in lateral prefrontal, striato-thalamic and temporo-parietal regions as well as in the cerebellum. Limitations in the studies include the use of ROI approach (Stevens, Pearlson, et al., 2007), the inclusion of different subtypes of ADHD (Konrad et al., 2006), of a significant proportion of comorbid cases (Konrad et al., 2006) or of patients with a previous history of stimulant medication (Stevens, Pearlson, et al., 2007; Tamm et al., 2006) within small samples.

2.3.3 Deficits during working memory processes

Verbal WM tasks in healthy subjects have shown to activate a cortical network including the DLPFC, key region involved in the storage and manipulation of the information and in the coding of the temporal sequence of stimuli (Amiez & Petrides, 2007; Owen, McMillan, Laird, & Bullmore, 2005), as well as the lateral IFC, temporo-parietal regions and cerebellum (Cabeza & Nyberg, 2000; Mayer et al., 2007; Owen et al., 2005; Volle et al., 2008).

Some differences between children with ADHD and healthy controls have been observed during the fMRI adaptations of various WM tasks. In the only study that has used the N-Back in paediatric ADHD populations, patients showed reduced activation compared to controls in left precentral cortex and IPL, in bilateral superior parietal lobes (SPL) and cerebellum (Kobel et al., 2009), as well as reduced responses compared to healthy controls in the 2-Back and 3-Back conditions (Kobel et al., 2009). However, the association between these performance differences and brain activation was not investigated.

Using a delayed match-to-sample verbal WM task, girls with ADHD showed reduced activation during high WM load in the right IFC/insula, as well as in right SPL (Sheridan, Hinshaw, & D'Esposito, 2007). The authors furthermore observed that in ADHD girls, activation in the left VLPFC was associated negatively with faster retrieval (Sheridan et al., 2007).

In the Visual Serial Addition Task (VSAT), a variation of the Paced Auditory Serial Addition (PASAT) (Gronwall, 1977), subjects are presented with the first number of a mathematical addition, and after a short delay they are presented with the

second number and the result, and need to press whether the result is correct or not. In this case, the authors used both whole brain and ROI methods (Fassbender et al., 2011). They identified enhanced activation in patients compared to controls in right IFC, putamen, insula bilaterally and left MFC, and only when using a ROI approach they observed enhanced WM-related activity in controls compared to ADHD patients in a different region of the left premotor cortex. Across all subjects, activation in the left putamen and bilateral insula was positively associated with longer RT, and within ADHD patients with the total ADHD symptoms score (Fassbender et al., 2011). However, the increased number of omission errors observed in ADHD patients was not significantly associated with any of the clusters of observed BOLD signal differences.

During visuo-spatial WM tasks, medication-naïve children with ADHD compared to controls have shown reduced activation in bilateral IFC and left SFC (Silk et al., 2005), caudate (Silk et al., 2005; Vance et al., 2007), in right STG (Silk et al., 2005) and in occipito-parietal regions (Silk et al., 2005; Vance et al., 2007). In addition, children with ADHD showed enhanced activation compared to healthy controls in left medial temporal gyrus (MTG) and STG, in PCC and in medial superior frontal cortex (Silk et al., 2005). Although these authors also observed reduced accuracy in the ADHD group compared to the group of healthy children (Silk et al., 2005), they did not investigate further the association between brain activation and performance differences.

The evidence therefore supports the presence of brain dysfunction especially in temporo-parietal regions, but also in MFC during WM tasks. However, the variety of tasks used, the small sample sizes (Fassbender et al., 2011; Kobel et al., 2009; Sheridan et al., 2007; Silk et al., 2005; Vance et al., 2007), the increased heterogeneity of the samples due to the inclusion of males and females (Fassbender et al., 2011), of different subtypes of the disorder or of comorbid conditions (Fassbender et al., 2011; Kobel et al., 2009; Sheridan et al., 2007; Silk et al., 2005; Vance et al., 2007) significantly complicates the interpretation of the findings.

2.3.4 Deficits during temporal processing tasks

In healthy subjects, fronto-striatal, parietal and cerebellar regions have been involved in temporal processing (Rubia, 2006; Rubia, Halari, Christakou, et al., 2009; Rubia & Smith, 2004; Wiener et al., 2010). The DLPFC and IFC have been directly

involved in time perception processes (Aso et al., 2010; Buetti, Walsh, Frith, & Rees, 2008; Coull & Nobre, 2008; Lewis & Miall, 2006b; Rao, Mayer, & Harrington, 2001; Rubia, 2006; Rubia & Smith, 2004; Shih, Kuo, Yeh, Tzeng, & Hsieh, 2009; Smith, Taylor, Brammer, Halari, & Rubia, 2008; Smith, Taylor, Lidzba, & Rubia, 2003; Wiener et al., 2010). SMA/pre-SMA and ACC have been associated with both the estimation of stimuli duration and fine temporal adjustment of the motor output (Buetti et al., 2008; Coull & Nobre, 2008; Coull, 2004; Macar et al., 2002; Rao et al., 2001; Rubia, 2006; Rubia & Smith, 2004; Shih et al., 2009; Smith et al., 2003; Wiener et al., 2010). In line with the hypothesis of dopaminergic regulation in temporal processes (Lewis & Miall, 2006a), striatum/basal ganglia have been considered as “time generators” (Aso et al., 2010; Buetti et al., 2008; Coull & Nobre, 2008; Koch, Oliveri, & Caltagirone, 2009; Lewis & Miall, 2006a; Rao et al., 2001; Shih et al., 2009; Shih, Yeh, Kuo, Tzeng, & Hsieh, 2010; Wiener et al., 2010). The cerebellum is furthermore a key region for timing processes (see Rubia & Smith, 2004 for a review,; and Wiener et al., 2010 for a meta-analysis), especially for those processes in the sub-seconds range (Aso et al., 2010; Rubia & Smith, 2004; Smith et al., 2003; Wiener et al., 2010).

Reduced activation in temporal processing brain networks has been reported in medication-naïve children with ADHD compared to controls during temporal discrimination tasks in bilateral OFC/ IFC (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008), right DLPFC (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008), caudate (Rubia, Halari, Christakou, et al., 2009), ACC/SMA (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008) and cerebellum (Rubia, Halari, Christakou, et al., 2009). Enhanced activation was also reported during a TD paradigm in children with ADHD compared to controls in dorsomedial prefrontal cortex and posterior temporo-occipital regions (Rubia, Halari, Christakou, et al., 2009). In previously medicated children with ADHD similar results have also been reported, with reduced activation relative to controls in the left ACC and posterior cerebellum, and reduced functional connectivity between right IFC and left cerebellum during a temporal discrimination task (Vloet et al., 2010).

During temporal synchronization and tapping tasks children with ADHD have shown underactivation compared to controls in ACC and PCC (Rubia, Overmeyer, et al., 1999), right superior parietal region (Mostofsky et al., 2006) and in a ROI analyses conducted in the same study from Mostofsky et al. (Mostofsky et al., 2006),

in the contralateral primary motor cortex. Also, enhanced activation has been reported in the right SMA (Rubia, Overmeyer, et al., 1999).

During a GNG task with a component of timing manipulation children with ADHD compared to healthy controls have shown reduced activation in the inferior cerebellum during unpredictable compared to predictable stimuli timing (Durstun et al., 2007; Mulder et al., 2008).

Finally, during temporal discounting tasks, measuring temporal foresight, reduced activation has been reported in children with ADHD in IFC/OFC, putamen, thalamus, PCC, parietal regions and cerebellum (Rubia, Halari, Christakou, et al., 2009). Furthermore, all the clusters of underactivation were associated with enhanced hyperactivity symptoms (Rubia, Halari, Christakou, et al., 2009)

Association between performance differences and brain activation differences has been reported so far by only one study, where children with ADHD showed a shorter RT for delayed reward choices (they deliberate shorter than controls when choosing delayed over immediate rewards), which was positively correlated with the reduced BOLD response observed in the cerebellum (Rubia, Halari, Christakou, et al., 2009). Although other studies have reported impaired performance in these tasks in children with ADHD, with errors during TD (Vloet et al., 2010) and reduced accuracy during temporal manipulations of stimuli in a GNG task (Durstun et al., 2007; Mulder et al., 2008), none of these studies tested for the association between these performance differences and between-group differences in BOLD response. So far, the only association between brain activation during time processing and ADHD symptoms has been reported by Rubia et al (Rubia, Halari, Christakou, et al., 2009), where there was an inverse association between the reduced activation in children with ADHD during temporal foresight showed in IFC/OFC, putamen, thalamus, PCC, parietal regions and cerebellum and hyperactivity symptoms (Rubia, Halari, Christakou, et al., 2009)

Thus, during motor timing, time estimation, time discrimination and temporal foresight processes, children with ADHD show consistently reduced activation compared to healthy controls in key areas that have consistently been associated with temporal processes, such as in IFC, DLPFC, SMA, ACC, striatum and cerebellum. However, as in all previous sections, findings need to be interpreted with caution given the restriction to the results imposed by the use of ROI methods by some of the studies (Mostofsky et al., 2006; Mulder et al., 2008; Vloet et al., 2010); the relatively

small sample sizes (Mostofsky et al., 2006; Mulder et al., 2008; Rubia, Halari, Christakou, et al., 2009; Rubia, Overmeyer, et al., 1999; Vloet et al., 2010) and the crucial confound which is the inclusion of previously medicated participants in some of the studies (Mostofsky et al., 2006; Mulder et al., 2008; Vloet et al., 2010). Thus, especially relevant is the evidence from studies on medication-naïve samples, which used whole brain analysis methods (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008).

2.3.5 Reward and motivation-related deficits

It is interesting that despite the fact that it has been hypothesised that abnormal reinforcement processing is key to ADHD (Luman et al., 2005; Luman et al., 2010; Sagvolden et al., 2005), there are very few studies that have tested for evidence on their potential neural underpinnings in children with ADHD. Thus, during the reward condition of a sustained attention task reduced activation has been reported in children with ADHD compared to controls in left PCC and precuneus (which was furthermore specific to children with ADHD when compared to children with CD) (Rubia, Smith, et al., 2009) and cerebellum (Rubia, Halari, Cubillo, et al., 2009). Enhanced activation in patients compared to controls has also been reported in a different sample of ADHD children, in OFC and temporal regions (Rubia, Halari, Cubillo, et al., 2009), which according to the authors was suggestive of enhanced sensitivity to rewards. Furthermore, reduced activation in children with ADHD relative to controls has been reported in right VS during reward anticipation (Scheres, Milham, Knutson, & Castellanos, 2007).

Thus, despite the reduced number of studies, the evidence is suggestive of abnormalities in OFC-striatal, PCC and cerebellar regions during reward-related processes in children with ADHD. However, more studies are needed.

2.4. ADHD and functional connectivity

Recent fMRI studies in ADHD have focused not only on the abnormalities observed in brain activation in specific brain regions, but also in the disrupted functional connectivity between these regions, both during the resting state and in the context of cognitive tasks.

During the resting state, reduced functional connectivity has been reported in children with ADHD compared to healthy controls in fronto-striatal, cingulate, fronto-

parietal, temporo-parietal and fronto-cerebellar networks, although some studies have also reported increased inter-regional connectivity between ACC, striatum and temporo-cerebellar regions (for reviews see (Konrad & Eickhoff, 2010; Liston et al., 2011)). Additionally, abnormalities in the default mode network (DMN) have also been reported. The DMN comprises midline structures including the ventromedial prefrontal cortex, PCC, and precuneus, is characterised by low-frequency oscillations of BOLD signal at rest (Raichle et al., 2001) and is typically anti-correlated with networks engaged by effortful cognitive tasks (Fox et al., 2005; Sonuga-Barke & Castellanos, 2007). Children with ADHD compared to healthy developing children showed decreased integration of the components of the DMN (Fair et al., 2009). Furthermore, problems with deactivation of the DMN have been linked to attention lapses in ADHD (Fassbender et al., 2009; Sonuga-Barke & Castellanos, 2007).

As mentioned above, few fMRI studies have focused so far on the abnormalities observed in functional connectivity in children with ADHD compared to healthy controls in the context of cognitive tasks. Thus, ADHD patients relative to healthy controls have shown reduced functional connectivity during sustained attention between IFC, basal ganglia, parietal cortices and cerebellum (Rubia, Halari, Cubillo, et al., 2009), during a TD task between right IFC and left cerebellum, and during interference inhibition between IFC and SPL (Vloet et al., 2010).

Therefore, children with ADHD show not only brain dysfunctions in isolated brain regions during disorder-relevant cognitive tasks but also reduced functional connectivity both during the resting state and in the context of cognitive tasks.

2.5 Findings from structural and functional studies in adults with ADHD

As a neurodevelopmental disorder, ADHD was considered until recent times a childhood disorder that resolved in late adolescence, hence the focus of imaging studies of ADHD was mostly in children. However, evidence has shown that symptoms of ADHD persist until adulthood in up to 65 % of the cases (Barkley et al., 2002; Biederman et al., 2006).

The evidence of structural and functional abnormalities in adult ADHD populations is less numerous, although suggestive of similar abnormalities as those described in children with the disorder. Thus, sMRI and DTI studies have provided evidence for structural abnormalities (reduced cortical thickness, volumes or grey and white matter volumes) in subcortical structures, as well as in DLPFC/IFC, ACC and

PCC, and temporo-parietal regions (see (Cubillo et al., 2012) and (Cubillo & Rubia, 2010) for reviews).

However, meta-analytic structural imaging studies as well as longitudinal imaging studies in children with ADHD have shown the normalisation of the reduced basal ganglia grey matter volumes with age, so that adults no longer showed deficits (Castellanos et al., 2002; Frodl & Skokauskas, 2012; Nakao et al., 2011). Therefore, there is evidence that basal ganglia deficits normalise in adult ADHD. Whether abnormalities normalise with age is a highly relevant issue that can only be studied with large samples in adequately designed prospective longitudinal studies.

It can therefore be concluded that patients whose symptoms of ADHD persist into adulthood show abnormalities in their brain structure that are similar to those reported in children with ADHD, most consistently in prefrontal, cingulate and temporo-parietal regions, as well as in subcortical structures with the exception of the basal ganglia (Cubillo et al., 2012; Cubillo & Rubia, 2010). However, prospective longitudinal follow-up studies into adulthood are needed to disentangle the association between brain structure abnormalities and symptomatic improvement or remission, as well as the influence of comorbid disorders, medication administration or different subtypes of ADHD into the persistence or severity of those structural abnormalities.

FMRI studies have also shown that, similarly to the evidence in childhood, adults with ADHD show reduced functioning during disorder-relevant cognitive tasks. Thus, adults with ADHD have shown reduced function compared to healthy control subjects in IFC and striatum during motor inhibition tasks, in ACC and fronto-striatal regions during interference inhibition, in dorsal/inferior prefrontal, temporo-parietal regions and subcortical structures (striatum/thalamus) during attention processes and in medial prefrontal and temporo-parietal regions during WM processes (for reviews, see Cubillo et al., 2012; Cubillo & Rubia, 2010). Some inconsistent results have also been reported, with enhanced activation during some tasks which may be potentially compensatory for the underactivated regions necessary to perform some cognitive processes, as it is the case with the enhanced occipital and cerebellar activation observed in Cubillo et al (Cubillo et al., 2012). However, from the review of the literature there seem to be a number of confounds that may complicate the integration and replication of findings (see Cubillo & Rubia, 2010 for a more detailed discussion on this issue). Some of these confounds are shared with the studies conducted in

children with ADHD, such as the small sample sizes, the presence of a significant number of participants with comorbid disorders or a previous history of stimulant medication, as well as the recruitment of mixed-gender samples. Furthermore, studies in adults typically include participants within a very wide age range (of up to 30 years), whose diagnosis of ADHD in childhood has been done retrospectively, which may be associated to recall bias (Cubillo et al., 2010). Thus, especially relevant are those studies where medication-naïve adults with ADHD have a confirmed childhood diagnosis of ADHD (Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011; Cubillo et al., 2012; Cubillo & Rubia, 2010; Makris et al., 2010). In these cases, the findings from adult and children patients with ADHD are remarkably similar, with reduced activation in dorsolateral fronto-striatal networks during cognitive switching and selective attention tasks, in ventromedial orbitofrontal regions during reward-related processing and in inferior frontal cortices and striatum during motor inhibition tasks (Cubillo et al., 2012; Cubillo & Rubia, 2010).

2.6. Summary and conclusions

As reviewed in the previous chapter, children with ADHD show deficits in a range of cognitive processes, most prominently during motor response inhibition, sustained attention, temporal processes, reward-related tasks and WM.

FMRI studies have provided compelling evidence of dysfunctions in children with ADHD in neural circuits underlying motor response inhibition, including right and left IFC, caudate and SMA/ACC, which in prefrontal regions has shown to be disorder-specific when compared to other paediatric disorders such as CD and OCD (Rubia, Cubillo, et al., 2010; Rubia et al., 2008).

Comparatively fewer studies have used attention-related paradigms, with particularly consistent evidence for underactivation in children with ADHD in temporo-parietal regions and the PCC across attention tasks. Disorder-specific dysfunctions for ADHD have also been described during attention allocation processes, in PCC when compared to OCD which was furthermore associated with ADHD symptoms (Rubia, Cubillo, et al., 2011), and in left IFC when compared to CD (Rubia, Halari, Smith, et al., 2009). Similarly, during sustained attention, ventrolateral prefrontal underactivation and enhanced activation in cerebellum and posterior brain regions were specific for ADHD compared to CD (Rubia, Smith, et al., 2009).

Also, relatively consistent deficits have been reported during WM tasks, especially when findings from visuo-spatial and verbal-auditory WM studies are considered together, the evidence suggests most consistently a pattern of underactivation in medial frontal regions and temporo-parietal cortices. However, given the impact that attention and verbal WM deficits may have in academic and school performance (Gathercole & Alloway, 2006), further research would be needed to clarify the brain function abnormalities underlying these deficits.

The evidence of dysfunction during temporal processes in ADHD patients is also relatively consistent, in particular during TD tasks, showing underactivation in children with ADHD relative to healthy controls in all the key areas within TD networks including bilateral IFC, SMA/ACC and cerebellum.

As reviewed above, the number of studies conducted on reward-related processing so far is very limited, but shows deficits in VS, PCC/precuneus and cerebellum and enhanced activation in OFC and temporal regions.

Despite the consistency of the findings, there are caveats that cannot be overlooked when reviewing the studies, including the small sample sizes, the recruitment of previously medicated children, the inclusion of patients with comorbid conditions, as well as mixed gender and mixed subtypes of ADHD samples. Furthermore, variations in the paradigms or methods used (such as the use of ROI or VBM methods) complicate the integration of the findings. These factors will be now separately reviewed.

It is recommended that for neuroimaging studies at least 20 subjects per group should be included to observe significant confident and replicable results (Thirion et al., 2007). However, there are few studies that included subjects of this or larger sample sizes, i.e. during motor inhibition (Rubia et al., 2008; Suskauer et al., 2008), attention (Rubia, Halari, Smith, et al., 2009; Stevens, Pearlson, et al., 2007) or TD paradigms (Smith et al., 2008). Only a few have included more than 15 subjects in each group during motor inhibition (Pliszka, Glahn, et al., 2006; Rubia, Cubillo, et al., 2010; Rubia et al., 2005; Smith, Taylor, et al., 2006), interference inhibition (Konrad et al., 2006; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Smith, et al., 2009; Smith, Taylor, et al., 2006), attention allocation (Rubia, Cubillo, et al., 2011; Rubia, Smith, et al., 2007b) or reward-related processes (Rubia, Smith, et al., 2009). Thus, the small samples sizes of the vast majority of the functional imaging literature needs

to be considered when interpreting the findings, and highlights the relevance of meta-analytic studies to integrate and provide consistent findings.

One of the most important factors in which studies differ is the inclusion of subjects with a previous history of stimulant medication. This is present in many of the reviewed studies (Booth et al., 2005; Durston et al., 2006; Durston et al., 2003; Epstein et al., 2007; Fassbender et al., 2011; Kobel et al., 2009; Mostofsky et al., 2006; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Prehn-Kristensen et al., 2011; Rubia, Halari, Christakou, et al., 2009; Scheres et al., 2007; Schulz et al., 2004; Schulz et al., 2005; Sheridan et al., 2007; Stevens, Pearson, et al., 2007; Suskauer et al., 2008; Tamm et al., 2006; Tamm et al., 2004; Vaidya et al., 2005; Vloet et al., 2010). Stimulant administration has shown long-term effects both on brain structure and function (Frodl & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009). This constitutes the most important confound in brain imaging studies in ADHD, since the observed abnormalities cannot be unequivocally attributed to the disorder, due to the potentially compensatory or other mechanisms triggered by the prescribed drug. Thus, specially valuable are those findings from the few studies where only medication-naïve children have been included (Konrad et al., 2006; Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Cubillo, et al., 2010; Rubia, Halari, Christakou, et al., 2009; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia, Smith, et al., 2007b; Rubia et al., 2005; Rubia, Smith, et al., 2009; Silk et al., 2005; Smith et al., 2008; Smith, Taylor, et al., 2006; Vance et al., 2007).

The integration and replication of the findings are also complicated by factors that increase the heterogeneity of the samples. One of these factors is the inclusion of patients with comorbid disorders in these small samples (at least 1/3 of the sample) (Kobel et al., 2009; Konrad et al., 2006; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Sheridan et al., 2007; Suskauer et al., 2008). Despite the well-known high rate of comorbid disorders (up to 75-85% in children with ADHD) (Biederman et al., 1991; Spencer, 2006; Wilens et al., 2002), the inclusion of patients with comorbid diagnosis should be avoided as it complicates the interpretation of the findings, especially in studies with such small sample sizes. Ideally, this should be avoided even in the case of the highly frequent comorbid diagnosis of ODD/CD, as it has recently observed the presence of shared but also disorder-specific dysfunctions

between these two disorders (Rubia, Halari, et al., 2010; Rubia et al., 2008; Rubia, Smith, et al., 2009)(for a review, see (Rubia, 2011)).

Furthermore, although most of the studies included only the combined subtype of the disorder, it is not unusual to find that studies have included different subtypes of the disorder in the already small ADHD samples, which increases their heterogeneity (Booth et al., 2005; Durston et al., 2007; Durston et al., 2003; Epstein et al., 2007; Kobel et al., 2009; Konrad et al., 2006; Mostofsky et al., 2006; Mulder et al., 2008; Schulz et al., 2004; Schulz et al., 2005; Sheridan et al., 2007; Suskauer et al., 2008; Vloet et al., 2010).

Similarly, the inclusion of males and females in the same sample group is a potential confound, given the gender-related differences in brain function, presentation of the disorder and brain maturation (Balint et al., 2009; De Bellis et al., 2001; Gershon, 2002; Mahone & Wodka, 2008; Rubia, Hyde, et al., 2010). It has also recently been reported that brain deficits were far more pronounced in males than females suggesting that mixed gender studies show reduced activation due to females overshadowing male deficits (Valera et al., 2010). Therefore, the inclusion of males and females conducted by some studies (Scheres et al., 2007) (Pliszka, Glahn, et al., 2006) (Booth et al., 2005; Durston et al., 2007; Durston et al., 2003; Epstein et al., 2007; Fassbender et al., 2011; Konrad et al., 2006; Mostofsky et al., 2006; Suskauer et al., 2008; Vaidya et al., 2005) may have masked or attenuated differences that, should the samples have been gender-homogeneous, would have been present.

We also need to take into account that although many studies have used whole brain methods to conduct the between-group comparisons, some have used a region of interest (ROI) approach (Durston et al., 2007; Durston et al., 2006; Epstein et al., 2007; Mostofsky et al., 2006; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Scheres et al., 2007; Schulz et al., 2004; Schulz et al., 2005; Suskauer et al., 2008; Vaidya et al., 2005; Vloet et al., 2010). Although justified when there is a strong apriori hypothesis, this approach may bias the results as it increases the statistical power to detect differences within those areas of interest, but it leaves aside other regions that may be playing a role in the disorder and have not been initially hypothesised as such (Friston et al., 2006).

Finally, another aspect that merits further attention is the presence of potential differences in IQ scores between children with ADHD and healthy participants, and how these differences are related to brain activation. To identify the role of IQ

differences between groups on cognition and brain activation two approaches are most commonly used.

On the one hand, groups can be matched for IQ scores, so that there are no significant differences between them. However, IQ scores have consistently been shown to be lower in patients with ADHD than in age-matched healthy controls (Bridgett & Walker, 2006; Kuntsi et al., 2004). Matching both groups according to their IQ would potentially recruit less impaired patients, not representative of the population studied, as they may show less pronounced cognitive and brain activation differences when compared to healthy subjects.

On the other hand, when groups differ in their IQ scores, those IQ scores are in many occasions used as a covariate, in an attempt to identify the role of IQ on the differences observed in brain activation between groups. However, this is controverted from the statistical point of view, as it is statistically inadequate. ANCOVA analyses should not be used to correct a between-group finding for a covariate that replicates the distribution of the classification variable, as it is the case in case-control studies, where participants are not randomly assigned to the groups. Given that patients with ADHD have shown to have lower IQ scores than healthy controls, this makes it inadequate the use of IQ as a covariate to rule out the effect of such differences in IQ on the brain activation differences observed between the two groups (Miller & Chapman 2001, Evans & Anastasio 2001, Dennis et al., 2009).

However, the findings from fMRI studies that do not control for the observed differences in IQ between-groups (Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 2005) or where IQ has been used as a covariate (Rubia, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009; Rubia, Smith, et al., 2009), are similar to those from studies where patients and healthy controls did not differ in IQ scores (Booth et al., 2005; Durston et al., 2007; Durston et al., 2006; Konrad et al., 2006; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Rubia, Cubillo, et al., 2011; Rubia, Cubillo, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia, Smith, et al., 2007b; Rubia et al., 2005; Scheres et al., 2007; Schulz et al., 2004; Schulz et al., 2005; Smith et al., 2008; Smith, Taylor, et al., 2006; Stevens, Pearson, & Kiehl, 2007; Suskauer et al., 2008; Tamm, Menon, & Reiss, 2006; Tamm et al., 2004; Vloet et al., 2010). Thus, the evidence suggests that the differences observed between children with ADHD and healthy controls in brain activation are

unlikely to be explained by the differences in IQ scores. However, it is perhaps necessary to incorporate the evidence from neuropsychological studies when considering the effects of IQ differences on cognitive function and brain activation, as these have shown that the role of IQ on the cognitive deficits observed in ADHD may differ depending on the cognitive function studied.

Thus, IQ has been shown to be moderately associated with inhibitory measures (Mahone et al., 2002), and the evidence from meta-analytic studies suggests this association may only partially underlie the deficits reported in children with ADHD during inhibitory functions, with IQ being only a borderline moderator of the differences observed during motor inhibition tasks (Lipszyc & Schachar, 2010; Willcutt et al., 2005). In line with this, the findings from fMRI studies using motor inhibition and interference inhibition tasks that do not control for the observed differences in IQ between-groups (Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 2005) or where IQ has been used as a covariate (Rubia, Halari, Cubillo, et al., 2011; Rubia, Cubillo, et al., 2010), are very similar to those from studies where patients and healthy controls did not differ in IQ scores (Booth et al., 2005; Durston et al., 2007; Durston et al., 2006; Konrad et al., 2006; Mulder et al., 2008; Pliszka, Glahn, et al., 2006; Rubia, Cubillo, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005; Schulz et al., 2004; Schulz et al., 2005; Smith, Taylor, et al., 2006; Suskauer et al., 2008; Tamm et al., 2004; Vloet et al., 2010), with reduced activation in key inhibitory areas, including the right VLPFC and striatum, but also in left VLPFC, ACC and SMA. Furthermore, some of the studies have reported their findings with and without using IQ as a covariate, and their results did not significantly differ (Liddle et al., 2010; Peterson et al., 2009; Rubia, Halari, Mohammad, et al., 2011). Thus, the evidence suggests that the differences observed between children with ADHD and healthy controls in brain activation during motor and interference inhibition tasks are unlikely to be explained by the differences in IQ scores.

On the other hand, measures of perceptual timing have been shown to vary with IQ scores (Paule, Chelonis, Buffalo, Blake, & Casey, 1999; Wearden, Wearden, & Rabbitt, 1997), suggesting that abnormal timing functions in ADHD might be associated with low IQ. This has been shown in children with ADHD during duration reproduction (Smith et al., 2002; Toplak et al., 2003), time estimation (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001), and temporal discounting tasks

(Bitsakou et al., 2009; Kuntsi, Stevenson, Oosterlaan, & Sonuga-Barke, 2001; Marco et al., 2009). While fMRI studies using time discrimination tasks have been conducted on samples where no differences in IQ scores were observed between healthy participants and ADHD patients (Mulder et al., 2008; Rubia, Halari, Christakou, et al., 2009; Rubia, Overmeyer, et al., 1999; Smith et al., 2008; Vloet et al., 2010), during the only fMRI study using a temporal discounting task, participants differed in their IQ scores and IQ was entered as a covariate in the analysis (Rubia, Halari, Christakou, et al., 2009). Reduced activation was in key areas for temporal foresight, including IFC/OFC, putamen, thalamus, PCC, parietal regions and cerebellum (Rubia, Halari, Christakou, et al., 2009), and the reduced activation was furthermore associated with symptoms of ADHD, which suggests those deficits were not associated with IQ but with ADHD (Rubia, Halari, Christakou, et al., 2009).

In contrast, WM tasks have shown to be closely associated with IQ measures, with indirect evidence suggesting they may share a common neurological basis, with the DLPFC being a key region (Conway, Kane, & Engle, 2003). WM is typically one of the factors obtained in tests of general intelligence and therefore covarying for IQ during this task would indeed mean covarying for any differences in WM that may exist between the groups. fMRI studies in ADHD samples have used a variety of WM tasks, and differ in their sample characteristics and medication status of the patients, which complicates the comparison of the data. However, in the only study where groups differing in IQ scores were recruited, IQ was used as a covariate in the analyses (Sheridan et al., 2007). However, the authors found reduced activation in prefrontal and parietal regions in ADHD patients relative to healthy controls (Sheridan et al., 2007), which parallels those findings from fMRI studies where no differences in IQ were reported between groups (Fassbender et al., 2011; Kobel et al., 2009; Silk et al., 2005; Vance et al., 2007).

Therefore, although the evidence suggests that generally the findings from fMRI studies in ADHD are not due to the potential differences in IQ scores between participants with ADHD and healthy controls, the role of the presence of IQ differences between groups on brain activation may vary depending on the cognitive process targeted by the study, which needs to be taken into consideration in the design of the analysis to be conducted.

2.7. Final remarks on structural and functional neuroimaging of ADHD

Despite the limitations of the available evidence, when considering the findings from neuropsychological and functional imaging finding together, it can be concluded that children with ADHD compared to healthy controls show cognitive deficits in EF and in the key regions underlying these deficits, which include:

a) deficits in motor response inhibition as measured by the SST and GNG tasks, with underfunctioning IFC, basal ganglia (mostly caudate) and ACC/SMA;

b) deficits during working memory processes, with reduced functioning in medial PFC and temporo-parietal regions;

c) deficits during temporal discrimination tasks, with underfunctioning of DLPFC/IFC, ACC/SMA and cerebellum.

The disorder-specific character of some of these dysfunctions in key inferior frontal and striatal regions in ADHD (Rubia, Cubillo, et al., 2011; Rubia, Cubillo, et al., 2010; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia, Smith, et al., 2009) constitutes an important step towards the identification of the underlying differential aetiology of the disorder. However, it will only be with the study of large homogeneous, comorbid-free, medication-naïve samples that a more precise delineation of the underlying brain dysfunctions associated with the cognitive deficits and symptoms of ADHD will be obtained.

Thus, for this study a group of 20 medication-naïve boys with ADHD combined subtype was recruited, without additional comorbid diagnoses, with the only exception of CD/ODD, present in 2 participants. The selection of boys with only the combined subtype reduced the heterogeneity of the sample. Differences in brain activation would be more difficult to detect with heterogeneous samples, with a high proportion of participants with additional comorbid disorders diagnoses or including males and females, as gender-related differences have been reported in brain function, presentation of the disorder and brain maturation (De Bellis et al., 2001; Gershon, 2002; Mahone & Wodka, 2008; Rubia, Hyde, et al., 2010; Valera et al., 2010). Furthermore, and most importantly, this study avoided any confounds related to long-term effects of stimulant medication by recruiting children with ADHD who have never received stimulant treatment, which is highly relevant as long-term effects of stimulant medication have been described on brain structure and function (Frodal & Skokauskas, 2012; Konrad et al., 2006; Nakao et al., 2011; Shaw, Sharp, et al., 2009).

We selected 3 paradigms where the evidence of cognitive deficits and reduced function of the underlying neural networks is consistent: the motor response inhibition Stop Signal Task, a temporal discrimination task, and an N-Back Working Memory task.

CHAPTER 3. EFFICACY AND MECHANISMS OF ACTION OF METHYLPHENIDATE AND ATOMOXETINE

In 1937, Charles Bradley was the director of the Emma Pendleton Bradley House, a neuropsychiatric hospital for children. To identify the neural basis of the disorders presented by patients, he performed pneumoencephalograms, which involve gas or air that is introduced into the spinal cord, producing severe headaches to his patients. In an attempt to improve these headaches, he administered Benzedrine to the children, an amphetamine-based drug, which had not effects on their headaches, however, they experienced significant improvements in their behaviour and school work, which they performed more readily and accurately (Bradley, 1937, 1950; Strohl, 2011). These studies were the basis for the development of the most commonly prescribed stimulant drug nowadays, Ritalin (Strohl, 2011). Ritalin (Methylphenidate - MPH) was first synthesised by Leandro Pannizzoni in 1944, marketed in 1954 (Lange et al., 2010) and approved for its use in children with ADHD by the Food and Drug Administration (FDA) in 1955, when the legal requirements of the knowledge of pharmacokinetics of the drugs was significantly lenient (Swanson & Volkow, 1998). Thus, relatively little is known about its mechanism of action in ADHD.

Atomoxetine (ATX) is the first non-stimulant medication licensed in 2002 by the Food and Drug Agency (FDA) for the treatment of ADHD patients. The history of ATX, although shorter, shows some parallels with that of MPH. As with MPH, ATX was initially intended for a different use, in this case as an antidepressant (Zerbe et al., 1985), although it was finally used for the treatment of ADHD patients. Although known to be a selective presynaptic norepinephrine transporter blocker (NET), its mechanism of action in ADHD is also relatively unknown, as was the case with MPH.

A number of studies have focused on the efficacy of ATX in ADHD patients. Thus, initial research showed the positive effect of Tomoxetine (later the name changed because of potential confusion with the cancer drug Tamoxifen) on ADHD symptoms described by adult patients (Spencer et al., 1998). Since then, studies have shown the effectiveness of ATX both in children and adults with ADHD. However, a longer time course is required for the positive behavioural effects to be observed, as while the effects of MPH are typically observed within 1-2 hours of administration

(Swanson & Volkow, 2002), ATX reaches its maximal clinical efficacy only after 10-12 weeks (Hazell et al., 2010; Montoya et al., 2009).

3. 1. Compared efficacy of MPH and ATX

The beneficial effects of MPH have long been described, and have shown to be relatively fast, with clinical effects observable after 1 hour and lasting between 4-5 hours (Greenhill et al., 2001; Swanson & Volkow, 2002). Studies of drug efficacy typically report either the number of subjects that show a decrease in symptoms (usually of >25% with respect to their baseline measures) as measured by a determined ADHD symptom scale (Hazell et al., 2010), or report the effect size of the decrease in symptoms (Greenhill et al., 2001; Hanwella, Senanayake, & de Silva, 2011). MPH has shown to significantly reduce symptoms in the hyperactivity/impulsivity and inattention domains, as well as oppositional and aggressive behaviours in >75 % of the patients, with moderate to large effect sizes (Greenhill et al., 2001) (The MTA Cooperative Group, 1999). However, the relatively short life of its effects means it is necessary to administer MPH several times a day, which may affect compliance due to potential missing doses. The development of long-acting stimulants, which have shown to be as effective as immediate release formulations (Wolraich et al., 2001), allowed for the patients to overcome these issues.

ATX has shown to peak at plasma levels after 1-2 hours of dosing (Farid, Bergstrom, Ziege, Parli, & Lemberger, 1985; Witcher et al., 2003). Taken once daily, ATX has shown to improve behaviours not only in the morning but also in the evening, which persisted after 24 weeks (Wehmeier, Dittmann, Schacht, Helsberg, & Lehmkuhl, 2009). ATX has shown to reduce symptoms of both inattention and hyperactivity/impulsivity however, full clinical efficacy defined as the reported improvement of 25% of the initial ADHD symptoms at presentation, measured using the ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHD-RS) is reached in approximately 75% of the cases at 10-12 weeks (Hazell et al., 2010; Montoya et al., 2009). This is in many occasions a difficult period of time for parents, teachers and the child, and has the potential negative effect of reducing compliance. This reduced compliance may be a contributing factor for the impression reported by clinicians that ATX may be less effective than MPH.

However, the evidence suggests that both drugs are equally effective in ADHD. A recent meta-analytic study reviewed those randomized clinical trials that had directly compared MPH (both long-acting and immediate release) and ATX administration (Hanwella et al., 2011). Given the different definitions of response rates used by the studies included, which varied between 25-50% reduction in scores in ADHD-RS and the Turgay DSM-IV Screening and rating Scale (T-DSM-IV-S), the authors used the standardized mean difference in ADHD-RS scale as a measure of effect size and report no significant differences between the effect sizes of MPH and ATX (Hanwella et al., 2011). However, when different formulae were considered separately, long-acting but not immediate release MPH seemed to be superior to ATX (Hanwella et al., 2011). Nevertheless, it is important to consider that this study included a large randomized controlled trial which followed up subjects only for 3 weeks (Kemner, Starr, Ciccone, Hooper-Wood, & Crockett, 2005), and given the above mentioned time course of the clinical efficacy of ATX (Hazell et al., 2010; Montoya et al., 2009), this may have resulted in an underestimation of its compared effectiveness. Another meta-analysis took this aspect into account and only included those trials that used sufficiently long durations as to observe clinical effects of ATX (Hazell et al., 2010). Similar clinically meaningful responses, defined as the reported improvement of 25% of the initial ADHD symptoms at presentation measured using the ADHD-RS scale, were reported for both MPH and ATX, with 70% of patients showing positive responses at 6 weeks and 77% at 10 weeks (Hazell et al., 2010 4342). Furthermore, when efficacy was defined at a more stringent level of >40% improvement in core symptoms compared to the baseline symptoms score on the ADHD-RS scale, similar improvements were reported for both ATX and MPH, with 54% of the cases showing positive responses, with a slightly higher proportion of responders for ATX at 10 weeks (67% vs 60% for MPH). These results were furthermore not affected by the inclusion/exclusion of patients with comorbid ODD, that is, comorbid ODD did not change the comparable efficacy rate for MPH and ATX (van Wyk, Hazell, Kohn, Granger, & Walton, 2012).

A negative aspect of ATX (shared by long-acting MPH) is its comparatively higher price relative to that of immediate-release MPH. The technical appraisal (TA98) from the National Institute for Clinical Excellence (NICE) on the use of MPH and ATX for the treatment of ADHD concluded that both drugs share a similar cost-effectiveness, however, it also highlighted the difficulty to make direct comparisons

(<http://publications.nice.org.uk>). A more recent UK-based study showed that the longer-lasting and more stable responses to ATX than MPH make ATX an adequate cost-effective drug, at least in the UK (Cottrell et al., 2008).

However, **adverse events** have been described both after MPH and ATX treatment. MPH has been associated with potential cardiac adverse events, including hypertension or sudden death cases (Graham et al., 2011). These have also been described with ATX, although to a lesser extent (Kelly et al., 2005). Thus, careful monitoring of risk factors and frequent cardiac reviews are recommended when MPH and ATX are prescribed (Graham et al., 2011). Another controversial area with regards to MPH administration is the potential for drug diversion, or the increased risk for potential substance use/abuse disorders (Biederman et al., 2008; Faraone, Biederman, Wilens, & Adamson, 2007), although this has shown to be possibly mediated by the presence of a comorbid diagnosis of conduct disorder (Barkley, Fischer, Smallish, & Fletcher, 2003). Nevertheless, the evidence is not conclusive and it is recommended that a non-stimulant medication like Atomoxetine is prescribed in high-risk cases (Graham et al., 2011).

Other adverse events that have been reported in the literature are the increase or first-appearance of tics after treatment with MPH or ATX, or sleep disturbances after MPH dosing (Graham et al., 2011). The NICE guidelines suggest that ATX may be preferred to stimulant medications in the case of pre-existing tics or Tourette Syndrome. However, given the inconclusive evidence, close follow-up of the patients has been recommended, independently of the medication prescribed (Graham et al., 2011).

Furthermore, although with pronounced individual variability, there is evidence of an effect of MPH on growth (1cm/year height, 1kg/year weight) at least during the 1-3 initial years of treatment (for reviews see (Pliszka, 2007) or (Graham et al., 2011)).

Finally, despite the positive results of ATX on patients with comorbid anxiety or depressive symptoms (Kratohvil et al., 2005), the FDA included in 2005 a black box warning for ATX, which informs about the risk of increased suicidality in children with ADHD taking ATX, which needs to be carefully monitored (www.fda.gov). In addition to the already mentioned potential cardiac adverse events, the most commonly reported side effects of ATX are decreased appetite, dizziness and dyspepsia (Kratohvil, Vaughan, Harrington, & Burke, 2003), which are typically

transient and can be managed with adequate titration procedures (Kratochvil et al., 2003). Although some cases of liver failure have been described, the evidence is not conclusive and therefore the recommendation is of close vigilance (Graham et al., 2011).

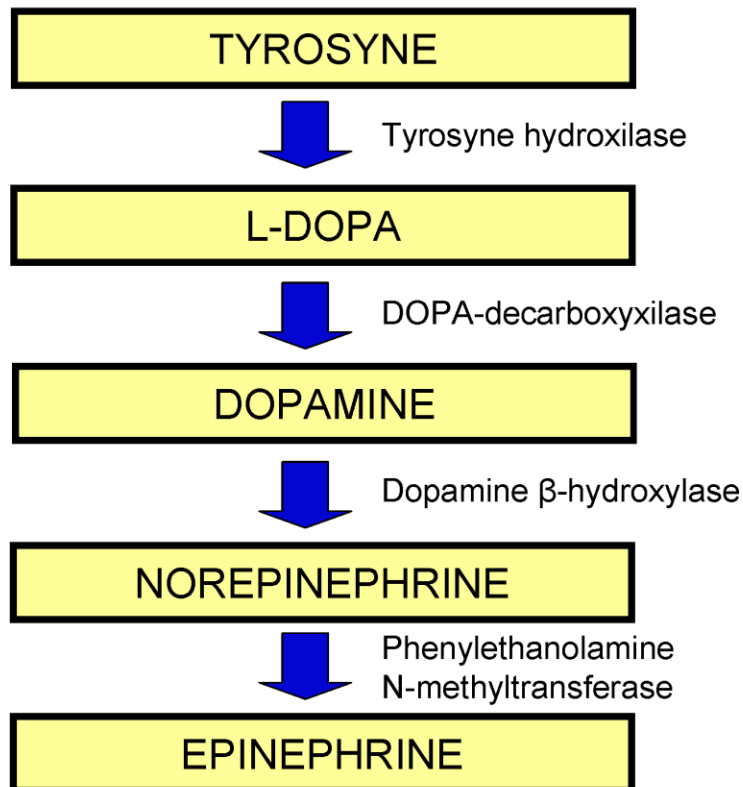
In conclusion, both drugs have shown similar efficacy in the treatment of ADHD symptoms in children with ADHD, reducing >25 % of the core symptoms of inattention and hyperactivity/impulsivity in 65-75% of ADHD patients (Hanwella et al., 2011; Hazell et al., 2010). However, their time courses significantly differ: while behavioural effects of MPH are observed shortly after administration (Swanson & Volkow, 2002), ATX reaches its maximal clinical efficacy after 10-12 weeks (Hanwella et al., 2011; Montoya et al., 2009). In both cases, a close monitoring of their potential adverse effects is required. The next sections of this chapter will review the evidence on their potential mechanisms of action on brain systems in ADHD, which are still relatively unknown.

3.2. Dopaminergic and noradrenergic abnormalities in ADHD

3.2.1. Catecholaminergic systems in the human brain

Dopamine (DA) and noradrenaline (NE) are catecholaminergic neurotransmitters with most prominently modulatory function on other neurotransmitter systems (Aston-Jones & Cohen, 2005). DA and NE are synthesised from the amino acid tyrosine and share a common biosynthetic pathway (Schwartz, 2000). Tyrosine is converted into L-Dopa by the enzyme tyrosine hydroxylase, which is present in limited amounts in the brain and therefore rate-limiting in the production of DA and NE (Figure 1). L-Dopa is then converted by the enzyme dopa-decarboxylase into DA, and this by the enzyme β -hydroxylase into NE. Finally, NE is converted by phenylethanolamine-N-methyltransferase into epinephrine (Figure 3.1).

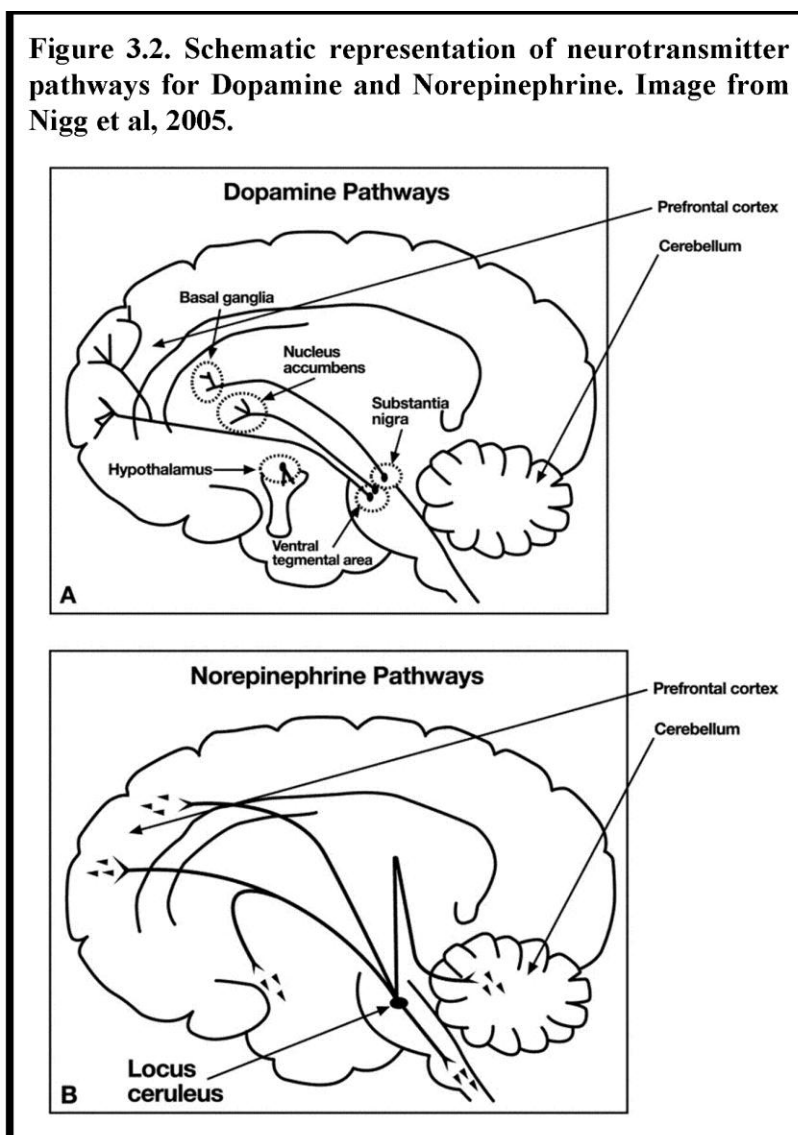
Figure 3.1. Biosynthetic pathway for Dopamine, Norepinephrine and Epinephrine



However, not all the catecholaminergic cells express all the enzymes and thus do not produce all the neurotransmitters. Thus, DA is synthesised in groups of midbrain neurons located mostly in the ventral tegmental area (VTA), the substantia nigra (pars compacta) (SN) and retrorubral area (Gerfen, 2010). There are four major dopaminergic tracts: 1) the nigrostriatal projection, formed by dopaminergic axons (mostly, but not only) which projects from the SN to caudate, putamen and nucleus accumbens (Moore & Bloom, 1978) and is involved in movement control (Robbins, 2010; Schwartz, 2000). 2) Dopaminergic neurons in the mesocortical tract project from the SN and VTA to cortical regions (Moore & Bloom, 1978). 3) The mesolimbic tract is formed by dopaminergic neurons from the SN and VTA which project to the amygdala and hippocampus, and both mesocortical and mesolimbic tracts are involved in EF, affect, emotion and motivation regulation (Robbins, 2010; Schwartz, 2000). Furthermore, some mesolimbic DA projections have been described in the thalamus and cerebellar vermis, regions traditionally considered as lacking dopaminergic projections (Melchitzky & Lewis, 2009). 4) The last dopaminergic tract

projects from the arcuate nucleus of the hypothalamus to the pituitary gland and regulates hormone secretion (Moore & Bloom, 1978; Schwartz, 2000) (Figure 3.2).

Figure 3.2. Schematic representation of neurotransmitter pathways for Dopamine and Norepinephrine. Image from Nigg et al, 2005.



Dopaminergic receptors can be grouped into two families according to their ligand-binding affinities and signal transduction mechanisms: D2/D3/D4 and D1/D5 receptors (Missale, Nash, Robinson, Jaber, & Caron, 1998). These have shown to be unevenly distributed in the brain. Thus, D1 receptors are present in the caudate, putamen, nucleus accumbens, and at lower levels in cerebral cortex, hippocampus, amygdala, thalamus and cerebellum (Hall et al., 1994; Melchitzky & Lewis, 2009). D2 receptors are highly present in the striatum, VTA and SN (Hall et al., 1994; Melchitzky & Lewis, 2009). D3 receptors are present mostly in limbic regions, such as the accumbens, and at much lower levels in the SN, VTA, thalamus, cortex and cerebellum, which have moderate to low levels of this receptor. In VTA and SN D2/D3 receptors are localised presynaptically, so their function involves the

regulation of DA synthesis and release of DA. On the other hand, D4 and D5 are much less expressed in the brain, with D4 detected in the SN, VTA, nucleus accumbens, hippocampus, amygdala and cortex, and D5 being the least expressed of all dopaminergic receptors, and located mostly in hippocampus, cerebellum and thalamus at low levels (Melchitzky & Lewis, 2009) (Table 3.1).

Table 3.1. Summary of the distribution of dopaminergic receptors in human and non-human primates brain		
RECEPTOR	HIGH LEVELS	MODERATE/ LOW LEVELS
D2	Striatum N Accumbens VTA SN	
D3	Limbic regions (inc N accumbens)	SN VTA Thalamus Cortex Cerebellum
D4	SN VTA N accumbens Hippocampus Amygdala Cortex	
D1	Striatum N accumbens	Hippocampus Thalamus Amygdala Cortex Cerebellum
D5		Hippocampus Thalamus Cerebellum

Norepinephrine is synthesised in the locus coeruleus (LC), which projects mostly to the cerebral cortex and dorsal thalamus (Melchitzky & Lewis, 2009; Moore & Bloom, 1979; Ramos & Arnsten, 2007), as well as to the cerebellum (Moore & Bloom, 1979), limbic system and spinal cord (Moore & Bloom, 1979). However, noradrenergic innervation in the cortex is uneven, and prefrontal regions are less heavily noradrenergically innervated than primary somatosensory or visual cortices (Melchitzky & Lewis, 2009). Also other areas receive noradrenergic projections, with

heavy innervation in amygdala and hypothalamus, and more moderate in the cerebellar cortex (Melchitzky & Lewis, 2009; Moore & Bloom, 1979)(Figure 3.2).

Two groups of noradrenergic receptors have been described, α and β , which at the same time are divided in two subgroups each α_1 and α_2 , as well as β_1 and β_2 (each of them is divided into different subtypes (for reviews, see Koziak & Bylund, 2007; Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006). Norepinephrine has the highest affinity for the α_2 receptor, lower affinity for the family of α_1 receptors, and even lower still for β -receptors. α_{2a} is the most common NE receptor in PFC (Ramos & Arnsten, 2007).

The LC-NE system has been associated with arousal and stimuli responsiveness (Aston-Jones & Cohen, 2005). Both noradrenergic and dopaminergic systems have shown an inverted-U mode of functioning, with too low or too high levels of DA and/or NE impairing cognitive function (Arnsten, 2009; Berridge et al., 2011; Robbins, 2010), which varies depending on the different cognitive function studied as different levels of neurotransmitters may be necessary (Arnsten, 2009; Cools & D'Esposito, 2011; Gamo, Wang, & Arnsten, 2010; Robbins, 2010).

Fronto-striatal dopaminergic systems show a stability/flexibility trade-off in the brain (Cools & D'Esposito, 2011). Optimal levels of DA on PFC (via their action on D1 receptors) allow for the stability of representations withheld in WM by inhibiting neural firing to irrelevant stimuli (Arnsten & Pliszka, 2011; Cools & D'Esposito, 2011), while these levels seem to be too low to engage dopaminergic activity in the striatum via D2 receptors. However, with higher extracellular DA levels, D2 receptors stimulation in the striatum facilitates flexibility and rapid updating of information (Cools & D'Esposito, 2011), while excessive D1 stimulation in the PFC suppresses firing both to relevant and irrelevant stimuli (Arnsten & Pliszka, 2011; Cools & D'Esposito, 2011).

Phasic responses of the LC-NE system have been associated with task-related behavioural responses, by acting as an attentional filter that selectively modulates the responsiveness of task-related cortical circuits (Aston-Jones & Cohen, 2005). Thus, moderate levels of NE on prefrontal regions improve cognitive functions via α_2 receptors stimulation (Arnsten, 2009; Arnsten & Pliszka, 2011; Ramos & Arnsten, 2007). However, at high NE levels (as happens under highly stressful conditions), there is an increase in the noradrenergic tone and an attenuation of phasic NE responses (Aston-Jones & Cohen, 2005), and the excess of extracellular NE engages

α_1 and β -adrenergic receptors that impairs PFC function (Arnsten, 2009; Ramos & Arnsten, 2007). However, this allows for posterior brain regions to control behaviour, mechanism that may have originally had a survival value (Ramos & Arnsten, 2007), as it facilitates highly distractible activity oriented to exploration (Aston-Jones & Cohen, 2005)

Dopaminergic and noradrenergic transmission are terminated in several ways. Dopamine and norepinephrine transporters (DAT and NET, respectively) are membrane transporters that control extracellular levels of DA and/or NE by their reuptake from the synaptic space into the presynaptic neuron (Gainetdinov & Caron, 2003). In prefrontal regions, given the much higher proportion of NET and the almost absent presence of DAT, NET reuptakes both DA and NE into the presynaptic neuron (Moron, Brockington, Wise, Rocha, & Hope, 2002; Yamamoto & Novotney, 1998). Furthermore, DA and NE are also removed from the synaptic space by enzymatic metabolism via catechol O-methyltransferase (COMT) or monoamine-oxidase (MAO) (Gainetdinov & Caron, 2003; Gerfen, 2010; Mannisto et al., 1992; Melchitzky & Lewis, 2009; for more extensive reviews of dopaminergic and noradrenergic systems and monoamine transporters, see Torres, Gainetdinov, & Caron, 2003).

As both systems regulate neural circuits underlying critical higher cognitive functions typically impaired in ADHD patients, including inhibition, attention or time processing, abnormalities in these catecholaminergic systems have been hypothesized to underlie or at least contribute to the disorder (Biederman & Spencer, 1999; Frank, Santamaria, O'Reilly, & Willcutt, 2007; Gonon, 2009; Prince, 2008; Sagvolden et al., 2005; Sergeant, 2000; Staller & Faraone, 2007; Tripp & Wickens, 2008). Dysfunction in these systems may involve reduced neurotransmitter synthesis or release, or abnormally early or late termination of the catecholaminergic transmission, which may be due to reduced/enhanced levels of reuptake transporters or altered sensitivity/density of the pre/postsynaptic receptors, and may in turn regulate dopaminergic and noradrenergic transmission.

As reviewed by Madras et al (Madras, Miller, & Fischman, 2005), the DAT is present perisynaptically in the neuron (cell bodies, dendrites and axons) rather than in the immediate synapse. The DAT not only reuptakes DA, but also regulates DA release, as has been reported in the SN (Madras et al., 2005). Thus, abnormally high levels of reuptake transporters would clear DA in excess and lead to a reduced dopaminergic tone (Madras et al., 2005). Furthermore, reduced synthesis and release

to the synaptic cleft, reduced sensitivity or availability of the receptors or increased levels of DAT in the synaptic cleft would reduce catecholaminergic transmission.

3.2.2. Dopaminergic and noradrenergic dysfunctions in ADHD

The study of dysfunctions in dopaminergic systems in ADHD has focused mostly on the striatum, as there are no tracers that are adequate for the study of DA or NE in cortical regions (Arnsten, 2009). Most of the studies have focused on the level or **availability of DAT** in patients with ADHD. As recently reviewed by del Campo et al (Del Campo, Chamberlain, Sahakian, & Robbins, 2011) PET studies have provided evidence of abnormalities in striatal DAT in ADHD patients, with initial results supporting the hypothesized high levels of DAT in basal ganglia/striatum (Cheon et al., 2003; Dougherty et al., 1999; Dresel et al., 2000; Krause, Dresel, Krause, Kung, & Tatsch, 2000; la Fougere et al., 2006; Larisch et al., 2006; Spencer et al., 2007; Spencer et al., 2005). However, more recent studies do not support this hypothesis. In fact, these studies have shown reduced striatal DAT availability in medication-naïve adults with ADHD compared to controls (Hesse, Ballaschke, Barthel, & Sabri, 2009; Volkow et al., 2009; Volkow, Wang, Newcorn, Fowler, et al., 2007), in the midbrain in adolescents with ADHD (Jucaite, Fernell, Halldin, Forssberg, & Farde, 2005), or no differences when compared to healthy control subjects (Jucaite et al., 2005; van Dyck et al., 2002) (for reviews, see Del Campo et al., 2011; Krause, 2008) (for a meta-analysis, see Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012). These differences in the findings may have been influenced by a number of confounds, such as the different composition and sizes of the samples, age differences or the use of radiotracers with different specificities (Del Campo et al., 2011). Most importantly, there is evidence that the previous history of stimulant medication may be an important confounder: a recent meta-analysis conducted in PET and SPECT studies in ADHD patients is particularly relevant (Fusar-Poli et al., 2012). This study reports an increased density of striatal DAT in ADHD patients compared to those of healthy controls. However, a meta-regression analysis showed that patients without a history of medication had significantly lower striatal DAT levels than healthy subjects, while long-term medicated patients had significantly higher levels of DAT relative to controls (Fusar-Poli et al., 2012), with the presence of medication accounting for 48% of the variance of the results. The findings suggest that long-term medication may lead to an upregulation of DAT levels in the basal ganglia. The

potential effect of MPH of increasing DAT density with continued exposure had been previously hypothesised (Madras et al., 2005). The results of the meta-analytic study are thus of particular relevance as they suggest that the high levels of DAT reported by some studies may be an adaptive response of the brain to a long-term history of medication which, as the authors highlight, is in line with the clinical evidence of the need of progressively higher doses of stimulant to maintain the clinical efficacy (Fusar-Poli et al., 2012). However, given that the study was cross-sectional, longitudinal studies within patients are needed to provide conclusive evidence about this potential causality mechanism.

However, abnormal striatal DAT levels “per se” are unlikely to be the primary dopaminergic disruption in ADHD (Volkow, Wang, Newcorn, Fowler, et al., 2007). Using PET, reduced availability of D2/D3 receptors in adults ADHD patients has been reported in left lateralised regions including the left caudate (Volkow et al., 2009; Volkow, Wang, Newcorn, Telang, et al., 2007), as well as the left nucleus accumbens, midbrain and hypothalamic regions, which were furthermore negatively correlated to inattention symptoms (Volkow et al., 2009). However, these results are not consistent with those reported in children and adolescents with the disorder, as studies have reported either no differences (Jucaite et al., 2005), or increased D2/D3 availability (Ilgin, Senol, Gucuyener, Gokcora, & Sener, 2001; Lou et al., 2004) relative to healthy controls. Furthermore, Ilgin et al (Ilgin et al., 2001) reported an association between high levels of D2 receptors available at baseline and a) symptomatic improvement after MPH and b) the degree of down-regulation by MPH (Ilgin et al., 2001), suggesting more pronounced effects of MPH in those subjects with more abnormal levels of striatal dopaminergic receptor availability.

Measures of DA synthesis can be obtained using [^{18}F]DOPA or [^{11}C]DOPA as radiotracers, as these are taken by the L-aminoacid transporter (located in the dopaminergic presynaptic neurons) as an analogue of DOPA and stored in storage vesicles, a step necessary and part of the DA synthesis process (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998; Fusar-Poli et al., 2012) (Figure 3.1). Decreased DA synthesis in the midbrain observed in medicated children with ADHD compared to healthy adolescents has also been reported, which was furthermore associated with increased symptoms of inattention (Forssberg, Fernell, Waters, Waters, & Tedroff, 2006). Also in adults with ADHD, reduced presynaptic dopaminergic function was reported in prefrontal regions, more markedly in medial and left PFC, and also

associated with childhood symptoms of ADHD retrospectively reported (Ernst et al., 1998). In a study using parallel groups, a downregulation in dopamine turnover was reported in ACC, putamen, amygdala and midbrain, with medication-naïve adults with ADHD showing lower DA synthesis than controls and long-term treated ADHD patients in bilateral striatum, insula and amygdala (Ludolph et al., 2008). However, some controversial results have been reported, with increased DA storage in the midbrain of previously medicated adolescents with ADHD (after 2 weeks off their usual psychostimulant medication) compared to those in healthy controls (Ernst et al., 1999). Reduced DAT function has shown to downregulate presynaptic DA storage and synthesis (Gainetdinov & Caron, 2003). Thus, if as suggested by the recent meta-analysis mentioned above (Fusar-Poli et al., 2012) long-term stimulant administration may increase DAT levels, it can be hypothesized that this would lead to an increase in presynaptic DA synthesis and storage. Thus, the small sample sizes of these studies make it necessary to replicate their results in larger samples.

So far, there are no studies on NE transmission in ADHD, given the lack of suitable radiotracers with adequate binding specificity characteristics (Logan et al., 2007), thus hampering the study of the potential abnormalities on the NE system in patients with the disorder. However, promising advances have recently been made in studies in non-human primates (Gallezot et al., 2011; Seneca et al., 2006; Takano, Gulyas, Varrone, Maguire, & Halldin, 2009) and in humans (Hannestad et al., 2010), which may help to the future advance in this field.

3.3 Mechanisms of action of methylphenidate and atomoxetine

3.3.1. Methylphenidate

3.3.1.1 Pharmacokinetics

MPH (*dl*-threo-methylphenidate) is a 50:50 racemic mixture of two enantiomers, *d*-threo-methylphenidate and *l*-threo-methylphenidate (Swanson & Volkow, 2002). While *d*-threo-methylphenidate has shown specific binding in the striatum, *l*-threo-methylphenidate binding has been shown to be non-specific (Ding et al., 1997). The evidence shows that the therapeutic effects of MPH are due to the effects of the *d*-threo-methylphenidate enantiomer (Ding et al., 1997; Markowitz & Patrick, 2008; Srinivas, Hubbard, Quinn, & Midha, 1992). MPH is metabolised into

ritalinic acid (inactive metabolite), and it has been shown to reach its peak plasma and serum levels 1-1.5 hours after oral administration (Chan et al., 1983; Swanson & Volkow, 2002), with a half-life of 3 hours (Swanson & Volkow, 2002). This relatively short half-life means it is necessary either to be administered two or three times a day, or sustained release formulations to be used. The usual dose for MPH is 0.3-0.7 mg/kg, rounded to the nearest 2.5/5 mg (Santosh & Taylor, 2000). Peak brain concentrations of MPH occurring between 1-2h after its administration (Swanson & Volkow, 2002; Volkow, Wang, Fowler, Gatley, et al., 1998), which corresponds with the time to reach behavioural effects (Volkow, Wang, Fowler, Gatley, et al., 1998).

3.3.1.2 Effects on extracellular levels of DA and NE: rodent studies

MPH has shown to block the DAT and NET at therapeutic doses (Hannestad et al., 2010; Volkow, Wang, Fowler, Gatley, et al., 1998). In vitro studies show that MPH has high affinity for the dopamine transporter (DAT), lower affinity for the norepinephrine transporter (NET) and minimum affinity for the serotonin transporter (SERT) (Bymaster et al., 2002; Gatley, Pan, Chen, Chaturvedi, & Ding, 1996).

3.3.1.2.1 Effects on extracellular levels of DA

Microdialyses studies in rats have shown the effects of MPH administration on extracellular levels of DA and NE in different brain regions. Thus, dose-dependent enhanced levels of extracellular DA in prefrontal cortex (PFC) have been reported after administration of MPH in rats (0.25-1mg/kg intra-peritoneal -i.p.-, 2 mg/kg orally) (Berridge et al., 2006), as well as in the striatum (caudate/putamen) (10, 20, 30 mg/kg, orally)(Kuczenski & Segal, 1997), and in PFC, nucleus accumbens and striatum (3mg/kg, i.p.) (Bymaster et al., 2002). However, MPH seems to enhance extracellular levels of DA in the nucleus accumbens only at high dosage. Thus, different studies have shown no effects on DA levels in the nucleus accumbens at low doses (0.25 mg/kg i.p) (Berridge et al., 2006; Kuczenski & Segal, 2001, 2002), while higher doses produced a significant increase in DA levels in the nucleus accumbens (0.5 mg/kg i.p., 2.5 mg/kg orally) (Berridge et al., 2006; Kuczenski & Segal, 1997, 2001, 2002; Schiffer et al., 2006).

Furthermore, MPH (up to 50 mg/kg, i.p.) administration to rats had no effect on the biosynthesis of DA in striatal synaptosomal DA (Kuczenski & Segal, 1975). PET studies in rats have shown decreased radioligand DAT binding in the striatum

(suggestive of increased synaptic DA) after MPH administration (5 mg/kg, i.p.) both in rats and primates (Schiffer et al., 2006), without changes in binding in cerebellum (Schiffer et al., 2006).

Similarly in mice, both a single dose (1,3, 10 mg/kg, i.p.) and chronic (3 mg/kg i.p.) MPH administration increased extracellular levels of DA in PFC (Koda et al., 2010), without effects on 5-HT extracellular levels in these regions (Koda et al., 2010). However, in the striatum, only the high dose (10 mg/kg) administered acutely increased extracellular levels of DA (Koda et al., 2010).

3.3.1.2.2 Effects on extracellular levels of NE

MPH has shown effects not only on extracellular DA levels, but also on NE levels, which may be of particular relevance to the therapeutic effect of MPH in ADHD. Thus, after intra-peritoneal administration of MPH in rats, dose-dependent enhanced levels of extracellular NE in PFC have been reported (Bymaster et al., 2002), which were larger than those of extracellular DA (Berridge et al., 2006). MPH (3mg/kg, i.p.) as well as in primary sensory cortical regions (1mg/kg, 5 mg/kg, i.p.)(Drouin, Page, & Waterhouse, 2006). Similarly, in the medial septal area, MPH at high doses (0.5 mg/kg) increased NE levels (Berridge et al., 2006).

MPH in enhanced extracellular levels of NE in the hippocampus in a dose-dependent manner rats (10, 20, 30 mg/kg, i.p.) (Kuczenski & Segal, 1997)(0.5 mg/kg/2.5 mg/kg, i.p.)(Kuczenski & Segal, 2001) (1, 2.5, 5 mg/kg, oral)(Kuczenski & Segal, 2002), without changes in extracellular concentrations of 5-HT in the accumbens/striatum (Kuczenski & Segal, 1997, 2001).

In mice, a single dose (1, 3, 10 mg/kg, i.p.) and chronic (3 mg/kg i.p.) MPH administration increased extracellular levels of NE in PFC (Koda et al., 2010), and only at high doses in the striatum, without effects on 5-HT extracellular levels (Koda et al., 2010).

In conclusion, studies in rodents show that MPH enhances extracellular levels of DA and NE in PFC, DA in the striatum and NE in the hippocampus in a dose-dependent manner, with effects on extracellular DA in the nucleus accumbens and on NE in the medial septal area only at higher doses.

3.3.1.3 PET studies in healthy adults and non-human primates

PET studies have typically been used to observe the effects of MPH on the dopaminergic system. The radiotracers used compete with endogenous DA to block the DAT, or to occupy dopaminergic receptors. Thus, a reduction in radiotracer binding after MPH administration is typically interpreted as an increase of extracellular DA, which competes with the radioligand to occupy DAT or D2/D3 receptors (Laruelle, 2000).

PET studies in baboons have shown that MPH infusion (0.5 mg/kg) reduced radioligand binding in the striatum but not in the cerebellum (Ding et al., 1994). In healthy adults, a single dose of MPH showed that administered at therapeutic doses (0.25 mg/kg –1 mg/kg, orally), blocks striatal DAT significantly in a dose-dependent fashion, with therapeutic doses (0.25 mg/kg) blocking 50% DAT in striatum (Volkow, Wang, Fowler, Gatley, et al., 1998). Furthermore, MPH (0.5mg/kg, ip) significantly blocked striatal DAT without effects in the cerebellum (Volkow et al., 1996). In addition, MPH has recently been shown to block significantly the NET in the LC, raphe nuclei as well as in the hypothalamus (Hannestad et al., 2010).

However, as mentioned above, the difficulties to find a suitable radiotracer have limited the research on how NET-blockade by MPH may affect the noradrenergic system in humans (Logan et al., 2007).

It has been hypothesized that by blocking DAT, MPH increases extracellular DA (Volkow et al., 2001), which acts on the presynaptic dopaminergic D2 receptors, decreasing the phasic release of DA by the neuron (Seeman & Madras, 1998; Seeman & Madras, 2002). It has also been postulated that MPH would enhance task-specific signalling, improve attention and performance in cognitive tasks by increasing signal-to-noise ratio on target neurons, due to decreased background firing rates of dopaminergic cells (Volkow et al., 2001). Furthermore, as DA is involved in detecting the saliency of stimuli (Horvitz, 2000), as well as in motivation and reward processes (Schultz, 1998; Tobler, Fiorillo, & Schultz, 2005), by increasing DA signalling, MPH would also enhance the salience of the stimuli and improve reward and motivation-related processing (Volkow et al., 2001; Volkow, Wang, Fowler, & Ding, 2005).

3.3.1.3.1. Effects on DAT and D2/D3 receptor availability

In ADHD patients, prolonged treatment with MPH has been shown to affect DAT density and availability. In untreated, newly diagnosed adults with ADHD SPECT studies have shown that prolonged treatment (3x5mg/day) with MPH reduced

the specific binding of the radiotracer in the DAT striatum (suggestive of reduced availability/density of DAT, as there is a reduced number of DAT sites) when compared to baseline (Dresel et al., 2000). Unfortunately, the authors did not report the length of the treatment in this study (Dresel et al., 2000). Similar results were described by Krause et al using SPECT in medication-naïve adults with ADHD after 4 weeks of MPH treatment (3x5mg/day) (Krause et al., 2000), as also in a SPECT study in medication-naïve children with ADHD after 3 months therapy with MPH (0.25-0.6 mg/kg/day) (Vles et al., 2003). A SPECT study in medication-naïve adolescents with ADHD and comorbid substance use disorder showed that 3 weeks treatment with MPH (week 1: 0.3 mg/kg/day; week 2: 0.7 mg/kg/day; week 3: 1.2 mg/kg/day) reduced DAT availability compared to baseline levels in caudate and putamen (reduced binding of the radiotracer) (Szobot et al., 2008), which was concomitant to the reported symptomatic improvement. A small (N=5) group of medication-naïve children with ADHD showed a reduction in DAT availability compared to baseline levels following 3 months of treatment with MPH (0.25-0.6 mg/kg/day) (Feron et al., 2005). After 9-20 months of treatment, MPH was withdrawn, and after 4 weeks off-MPH, DAT activity levels returned to baseline levels, which suggested is no long-term effect of MPH on DAT availability (Feron et al., 2005).

Thus, the findings suggest that short-term treatment with MPH reduced DAT levels in medication-naïve children and adults with ADHD. However, results from recent meta-analysis conducted by Fusar-Poli et al (Fusar-Poli et al., 2012) using a meta-regression analysis showed that long-term medication history was associated with increased DAT levels. Therefore, differences between long-term and short-term effects of stimulant medication administration on DA system in ADHD patients that need to be further investigated.

The ability of MPH to reduce DAT availability has furthermore been associated with **symptomatic improvement** in several SPECT studies. In medication-naïve adults with ADHD, increased DAT availability compared to healthy subjects at baseline was associated with symptomatic improvement after 10 weeks of treatment with MPH (as measured by the Clinical Global Impression Scale – CGI, MPH was titrated up to 60 mg/day), which was taken as a proxy for response to MPH (Krause, la Fougere, Krause, Ackenheil, & Dresel, 2005; la Fougere et al., 2006). Thus, increased DAT availability at baseline seems to be a predictor of good response to MPH (Krause, 2008). However, Cheon et al (Cheon, Ryu, Kim, & Cho, 2005)

observed that, in a group of medication-naïve children with ADHD, those responsive to 8 weeks of MPH treatment (0.3-0.7mg/kg/day)(defined at 50% reduction in the ADHD Rating Scale) presented with lower striatal DAT levels at baseline (Cheon et al., 2005).

It has been shown the lack of association between the reduced binding of radioligands in DAT after single dose MPH challenge (60mg, orally) and the increase in extracellular DA levels (Volkow, Wang, Fowler, Logan, Franceschi, et al., 2002). The effects of MPH may not depend exclusively on DAT blockade, but also on other factors such as baseline levels of DA release (Volkow et al., 2001; Volkow, Wang, Fowler, Logan, Franceschi, et al., 2002). It has therefore been suggested that at a given DAT blockade level, MPH effects would be more significant in those subjects with higher activity in DA cells (releasing more DA) than in those with lower DA cell activity (Volkow, Wang, Fowler, Logan, Franceschi, et al., 2002).

PET studies using the radiotracer [^{11}C]Raclopride focus on the effects of MPH on extracellular levels of DA by measuring changes in striatal **D2/D3 receptor availability**. Post-stimulant administration decline in radioligand receptor-binding is indicative of reduced receptor availability, which suggests a pharmacologically evoked increase in extracellular DA. Thus, single dose MPH administration in healthy adults (60 mg, orally) (Volkow et al., 2001) and prolonged (12-months) treatment with MPH (~1 mg/kg/day, orally) in medication-naïve adults with ADHD (Volkow et al., 2012), have been shown to reduce the availability of striatal D2 receptors. Similarly, in medication-naïve children with ADHD, a single dose MPH challenge (0.3 mg/kg, orally) reduced the striatal binding of the radioligand (Rosa Neto, Lou, Cumming, Pryds, & Gjedde, 2002; Rosa-Neto et al., 2005). However, in adults with ADHD, a blunted response of the dopaminergic system has also been observed, with reductions in availability of striatal D2/D3 receptors after a single dose of MPH (0.5 mg/kg, i.p.) that were less pronounced than those in healthy controls (Volkow, Wang, Newcorn, Telang, et al., 2007).

PET studies in humans have also shown some effects of MPH on cortical regions. Thus, prolonged MPH treatment (1 mg/kg/day, orally) in adults with ADHD has been shown to increase extracellular DA in frontal and temporal regions (Volkow et al., 2012), while single dose MPH administration (40-60 mg, orally) in healthy adults reduced binding of the radioligand in a dose-dependent manner in frontal lobe, temporal cortex and thalamus, without significant changes in the

amygdala/hippocampus, ACC and cerebellum (Montgomery, Asselin, Farde, & Grasby, 2007).

Like with DAT levels, the changes induced by MPH administration in D2/D3 receptor availability have also been associated with **symptomatic improvement**. Medication-naïve adults with ADHD showed blunted responses to a single dose of MPH (0.5 mg/kg, i.p.) compared to controls (as measured by the occupancy of striatal D2/D3 receptors in the caudate by a radioligand), which were associated with more inattention symptoms in the Conners Adult Attention Rating Scale (CAARS) (Volkow, Wang, Newcorn, Telang, et al., 2007). Similarly, increases in extracellular DA levels after a single dose MPH challenge in the striatum in adults with ADHD who had undergone 12-months of treatment with MPH (~1mg/day, orally) were associated with symptomatic improvement in the inattention domain (Volkow et al., 2012).

Changes in striatal D2/D3 receptor availability have also been associated with performance during cognitive tasks. Thus, the reported reductions in D2/D3 receptor availability in the striatum in medication-naïve children with ADHD after a single-dose of MPH (0.3 mg/kg, orally) were positively associated with the baseline number of omission and commission errors, RT and SD of RT in a CPT-like task, suggestive of a stronger effect of MPH on blocking DAT in those patients who were more inattentive and impulsive (Rosa Neto et al., 2002; Rosa-Neto et al., 2005). According to the authors, these findings suggest that the effects of MPH on increasing striatal extracellular DA levels are more pronounced on those subjects with higher impulsivity levels as shown by their performance on the attention task. Furthermore, in healthy adults, the reduced availability in D2/D3 receptors in the striatum after a single dose of MPH (60 mg, orally) was associated with better performance during a spatial WM task and with poorer performance in a reversal learning task (Clatworthy et al., 2009).

It is therefore suggested that MPH would have stronger effects in those subjects where baseline activity in dopaminergic cells is high than in those where the activity in dopaminergic cells is low (Volkow, Wang, Fowler, Logan, Franceschi, et al., 2002). The increase of extracellular DA levels as a result of DAT blockade stimulates DA autoreceptors that attenuate DA release, thus decreasing dopaminergic background firing (noise), and improving signal-to-noise ratio in target neurons (Volkow et al., 2001). The amplification of weak DA signals experienced by ADHD

patients after MPH administration would enhance the saliency of the stimuli by enhancing task-specific signals, thus improving attention and performance (Volkow et al., 2001). In line with this, a single dose of MPH (20 mg, orally) in healthy adults enhanced extracellular DA levels in the striatum only during the performance of a remunerated mathematical task but not during a non-remunerated passive neutral task (Volkow et al., 2004), which was also found during presentation of food stimuli compared with presentation of neutral stimuli (20 mg, orally) (Volkow, Wang, Fowler, Logan, Jayne, et al., 2002). These DA increases were furthermore accompanied by the perception of increased saliency of both the food as well as the mathematical task (Volkow, Wang, Fowler, Logan, Jayne, et al., 2002; Volkow et al., 2004).

3.3.1.3.2 MPH and blood flow and metabolism in healthy subjects

PET studies in healthy adults have shown that MPH administration (two sequential doses: 1st 0.5 mg/kg, 2nd 90 minutes later, 0.25 mg/kg, both i.p.) has an effect on glucose metabolism in the brain, increasing cerebellar metabolism and decreasing glucose metabolism in the basal ganglia relative to the whole brain (Volkow, Wang, et al., 1997). It was furthermore observed that regional glucose metabolism changes in frontal and temporal cortices, as well as in cerebellum were associated with D2 receptor availability, with increased metabolism in those subjects with high D2 receptor availability and decreased metabolism in those adults with low D2 receptor availability (Volkow, Wang, et al., 1997).

A recent study using pattern recognition analyses has furthermore shown the compared effects of single doses of MPH (30 mg, orally) and ATX (60 mg, orally) on rCBF in healthy adults at rest (Marquand et al., 2012). The results suggest that MPH and ATX had effects in line with the DAT and NET distributions in the brain. Thus, compared to each other, MPH showed differential effects on rCBF in areas that are rich in DAT distribution such as the caudate, midbrain and SN, thalamus, ventromedial prefrontal cortex (VMPFC), cingulate cortex, insula and temporal lobes (Marquand et al., 2012). ATX on the other hand, showed differential effects on rCBF relative to MPH in areas that are rich in NET such as cerebellum, parahippocampal gyrus, posterior insula, inferior and medial frontal regions, sensorimotor and middle temporal cortices (Marquand et al., 2012).

The effects of MPH on task-related blood flow have also been studied in ADHD patients using PET. These studies will be reviewed in the next chapter, which gathers the available evidence on the effects of MPH and ATX on brain function in ADHD patients.

3.3.2. Atomoxetine

3.3.2.1 Pharmacokinetics

ATX is highly bound to plasma protein (Sauer et al., 2003), and is metabolised by the CYP2D6 enzyme into 2 metabolites: the active metabolite 4-hydroxyatomoxetine and the inactive metabolite N-desmethyatomoxetine (Ring, Gillespie, Eckstein, & Wrighton, 2002). The main metabolite 4-hydroxyatomoxetine, which has been described as pharmacologically active as the parent compound, has also a selective effect on blocking the NET, and may therefore contribute to the effects of ATX. However, in children, plasma concentration of this metabolite has been shown to be significantly lower compared to those of ATX (parent-to-metabolite ratio)(Witcher et al., 2003).

In children with ADHD, ATX has shown a similar pharmacokinetic profile both after a single dose and repeated administration of ATX (Witcher et al., 2003). Peak plasma levels of ATX are dose-dependent and reached after 1-2 hours of dosing (Farid et al., 1985; Witcher et al., 2003) with a plasma half-life of 3-4 hours (Witcher et al., 2003). ATX has shown similar pharmacokinetic profiles both in children and adults (Sauer et al., 2003; Witcher et al., 2003). Two polymorphic forms exist for the enzyme CYP2D6, and thus subjects can be subgrouped as rapid/extensive or slow metabolizers, which has shown to have an impact of the half-life of the drug (which may vary between the 5 hours described in extensive metabolizers to 22 hours in poor metabolizers) (Farid et al., 1985; Ring et al., 2002; Sauer et al., 2003). However, there is no clear evidence about differences in efficacy depending on the CYP2D6 polymorphism.

3.3.2.2 Effects on extracellular levels of DA and NE: rodent studies

ATX is a selective presynaptic NET blocker, with higher affinity for the NET than for SERT or DAT (Bymaster et al., 2002), and which blocks the NET almost

completely in the ACC, thalamus, brain stem, midbrain, LC and cerebellum (Ding et al., 2009; Gallezot et al., 2011; Takano et al., 2009).

In the PFC, the NET takes up DA into NE neurons, given the low density of DAT in this region and the high affinity of DA for NET (Moron et al., 2002; Sesack, Hawrylak, Matus, Guido, & Levey, 1998; Yamamoto & Novotney, 1998). Therefore, a noradrenergic reuptake inhibitor will also have enhancing dopaminergic effect in this region, but not in other DA-rich regions like the striatum, where DA is reuptaken by DAT.

3.3.2.2.1 Effects on extracellular levels of DA

Microdialysis studies in rats have shown that ATX (0.3-3mg/kg i.p.) increases extracellular levels of DA in PFC (Bymaster et al., 2002; Swanson et al., 2006), but not in the nucleus accumbens, striatum (Bymaster et al., 2002; Swanson et al., 2006), lateral hypothalamus or occipital cortex (Swanson et al., 2006). Furthermore, no effects on extracellular levels of 5-HT in the PFC were reported (Bymaster et al., 2002). Similarly in mice, a single dose (0.3, 1, 3 mg./kg, i.p.) and chronic (1 mg/kg i.p.) ATX administration increased extracellular levels of DA in the PFC (Koda et al., 2010), without effects in the striatum (Koda et al., 2010).

3.3.2.2.2 Effects on extracellular levels of NE

Microdialysis studies in rats have shown that ATX (0.3-3mg/kg i.p.) increases extracellular levels of NE in PFC (Bymaster et al., 2002; Swanson et al., 2006), as well as in the lateral hypothalamus, hippocampus and cerebellum (Swanson et al., 2006), without increasing extracellular levels of 5-HT in the PFC (Bymaster et al., 2002). Similarly, a single dose (0.3, 1, 3 mg./kg, i.p.) and chronic (1 mg/kg i.p.) ATX administration in mice increased extracellular levels of NE in the PFC (Koda et al., 2010), without effects in the striatum (Koda et al., 2010) or on 5-HT levels on these regions. Furthermore, the authors report a decrease in baseline extracellular levels of NE but not of DA in PFC after 21 days treatment with ATX, suggestive of adaptive processes in the brain to prolonged ATX administration (Koda et al., 2010).

In conclusion, rodent studies have shown that ATX increases extracellular levels of DA in the PFC, and of NE in PFC, lateral hypothalamus, hippocampus and cerebellum.

3.3.2.3 PET studies in healthy adults and non-human primates

As previously mentioned, PET studies on the effect of MPH and ATX on noradrenergic transporters have been hampered due to the lack of a suitable radioligand (Del Campo et al., 2011; Logan et al., 2007). However, some preliminary evidence of the effects of ATX on NET-rich areas has been provided by studies using sub-optimal radioligands in human and non-human primates, which will be reviewed below.

Studies in non-human primates have shown that clinical doses of ATX significantly occupy the NET almost completely in a dose-dependent manner in monkeys (Ding et al., 2009). Dose-dependent occupancy of ATX has also been reported in a PET study in monkeys in the thalamus, brainstem and anterior cingulate, where clinical doses of ATX occupy the NET almost completely (Takano et al., 2009). Similarly, a study focused on the use of a new radioligand to assess NET occupancy by ATX in non-human primates, showed that ATX blocks NET significantly in the ACC, thalamus, midbrain or brain stem, and furthermore suggested the use of the caudate as a reference region given the low NET binding (Gallezot et al., 2011).

A recent study using single-unit recording techniques in the DLPFC of monkeys while performing a spatial WM task showed that ATX enhanced activity in a inverted-U dose-dependent response fashion, by enhancing neuron firing for the preferred direction via $\alpha 2$ -adrenoreceptors and, to a lesser extent, also by decreasing neuronal firing for non-preferred directions (via D1 receptors). Thus, it increases “signal-to-noise” signal in DLPFC (Gamo et al., 2010).

The evidence of the effect of ATX in humans using PET is very limited. ATX has been shown to block NET in midbrain/locus coeruleus, brain stem, hypothalamus, thalamus, cingulate gyrus and cerebellum (Logan et al., 2007). However, the authors were not able to detect differences between the doses of ATX administered (25mg, 50mg or 100 mg). They suggest this might be due to non-specific NET background binding of the ligand used, highlighting the importance of the radioligand used (Logan et al., 2007). Another inconsistency of PET studies on NET is the use of an appropriate reference region with low NET density, which is crucial for the accuracy and replicability of the findings, with suggestions for the use of caudate or caudate+putamen (Logan et al., 2007), or the composite reference region of basal ganglia and occipital cortex (Logan et al., 2005).

Finally, the study from Marquand et al (Marquand et al., 2012) needs to be mentioned briefly again. As described above, the authors used pattern recognition analyses and showed differential effects of a single dose MPH (30 mg, orally) and ATX (60 mg, orally) on rCBF in healthy adults at rest (Marquand et al., 2012). While MPH showed differential effects on rCBF in the caudate, midbrain and SN, thalamus, VMPFC, cingulate cortex, insula and temporal cortices, ATX showed differential effects in cerebellum, parahippocampal gyrus, posterior insula, inferior and medial frontal regions, sensorimotor and middle temporal cortices (Marquand et al., 2012).

3.4 Conclusions

This chapter has shown the evidence for the comparable efficacy of both MPH and ATX in the treatment of ADHD symptoms, reducing >25% of the core symptoms of inattention and hyperactivity/impulsivity in 65-75% of ADHD patients (Hanwella et al., 2011; Hazell et al., 2010). Despite the fact that both are routinely prescribed for the treatment of ADHD, their mechanisms of action are still relatively unknown. From the evidence reviewed above, it can be concluded that MPH blocks the DAT in the striatum in a dose-dependent manner, as well as NET in the PFC, hippocampus, primary sensory regions, LC, raphe nuclei and hypothalamus. Meanwhile, ATX significantly blocks NET in PFC, hypothalamus, hippocampus, cerebellum, thalamus, brain stem, anterior cingulate and midbrain.

However, how the DAT and NET blockade improves or normalises catecholaminergic abnormalities and ADHD symptoms is still under study. The evidence on the dysfunctions of the dopaminergic system in ADHD is inconsistent. Initial studies showed that ADHD patients had higher levels of striatal DAT (Dougherty et al., 1999; Dresel et al., 2000; Krause et al., 2000; la Fougere et al., 2006; Larisch et al., 2006; Spencer et al., 2007; Spencer et al., 2005), which would reuptake DA from the synaptic space in excess, leading to a reduced dopaminergic tone. However, a large body of evidence does not support this statement, and reduced DAT levels have been described, in particular in larger sampled, better defined, medication-naïve and non-comorbid samples (Hesse et al., 2009; Jucaite et al., 2005; van Dyck et al., 2002; Volkow et al., 2009; Volkow, Wang, Newcorn, Fowler, et al., 2007). As reviewed above, a recent meta-analytic study provides evidence that the DAT levels may be dependent on long-term stimulant medication, being reduced in medication-naïve but enhanced in previously medicated ADHD patients. This

suggests potential mediating effects of previous MPH administration on the reported increase on DAT levels (Fusar-Poli et al., 2012), potentially as an adaptive response of the brain. It is important to note that in addition to the potential effects of long-term stimulant treatment other environmental factors may influence DAT levels and need to be considered in studies in children and adults with ADHD, such as smoking habits (Krause, 2008) or age-related changes in the dopaminergic system (Volkow, Wang, Fowler, Ding, et al., 1998; Wong, Young, Wilson, Meltzer, & Gjedde, 1997).

In addition, if MPH acts by blocking the DAT in the striatum, one can expect that to be directly associated to the increased level of extracellular DA. However, the available evidence suggests this is not the case (Volkow, Wang, Fowler, Logan, Franceschi, et al., 2002), and therefore other factors such as the rate of DA release or the availability or density of dopaminergic receptors may play a role on the effects of MPH on the dopaminergic system.

Furthermore, the evidence seems to suggest an association between the increase in extracellular DA levels as a consequence of DAT blockade by MPH and the symptomatic improvement in ADHD patients (Krause et al., 2000; la Fougere et al., 2006; Szobot et al., 2008; Volkow, Wang, Newcorn, Telang, et al., 2007; Volkow et al., 2012).

A different question is the effect of the enhanced extracellular dopaminergic levels in the brain. The elevated extracellular DA may reduce the phasic discharge in DA pathways (Seeman & Madras, 2002). Follow-up studies have shown that prolonged MPH administration in medication-naïve ADHD patients significantly reduces DAT availability levels, which were furthermore associated with symptomatic improvement. It may be that this reduced availability triggers adaptive processes in the brain, leading to an increase in DAT levels as a result of such processes, which would be in line with recent evidence from a meta-analytic study (Fusar-Poli et al., 2012). Furthermore, in medication-naïve ADHD patients reduced DA storage and synthesis have been reported, which may be linked to the known association between reduced DAT function that downregulates presynaptic DA storage and synthesis (Gainetdinov & Caron, 2003). Thus, if MPH significantly blocks DAT and the brain responds by increasing DAT levels in an attempt to regulate, that would lead to upregulated DA storage and synthesis, as reported by studies in adults and adolescents with ADHD (Ernst et al., 1999).

However, as suggested by the studies from Volkow et al, the effects of MPH may be context-dependent, as the enhanced DA levels would reduce background DA firing thus reducing noise and making relevant stimuli more salient, leading to enhanced salience of stimuli by increasing signal-to-noise ratio (Volkow, Wang, Fowler, Logan, Jayne, et al., 2002; Volkow et al., 2004). Thus, the beneficial effects of MPH may be due to the improved efficiency of the dopaminergic system in those contexts (whether these are classroom work or cognitive tasks in the lab) where the dopaminergic system of ADHD patients was previously dysfunctional (Volkow et al., 2005).

It is important at this time to note that MPH not only acts on dopaminergic but also on noradrenergic systems. Studies in animals suggest a combined action of MPH and ATX on both dopaminergic and noradrenergic systems as underlying the increased “signal-to-noise” ratio reported in the PFC during WM processes (Gamo et al., 2010). However, the field is greatly limited at the moment. Imaging the NET has shown to be complicated given the difficulties to develop adequate radioligands (Logan et al., 2007), with some recent success (Ding et al., 2009; Gallezot et al., 2011; Seneca et al., 2006; Takano et al., 2009). Similarly, only D2/D3 receptors in the striatum can be confidently studied due to lack of specific radioligands for other dopaminergic receptors, present in cortical regions (Melchitzky & Lewis, 2009). Furthermore, different radioligands used in different studies may have different binding-specificities and therefore may differ in their findings (Del Campo et al., 2011).

The evidence on the effects of ATX on the dopaminergic and noradrenergic systems is scarce. From rodent studies, we know that ATX enhances DA and NE in PFC, and NE in lateral hypothalamus, hippocampus and cerebellum. Also, PET studies in non-human primates and healthy adults have shown that ATX blocks the NET in NET-rich areas including thalamus, hypothalamus, ACC, brain stem/midbrain and cerebellum.

However, it is not known whether patients with ADHD present with abnormalities in the NE system which may be ameliorated by the administration of MPH or ATX, what are their differential effects or how the effects of ATX on dopaminergic or noradrenergic systems in the brain are associated with symptomatic improvement. The development of a radioligand with highly specific binding

characteristics for the NET will allow for the accurate measure of variations in the NE system after administration of MPH and ATX, which is crucial to clarify this area.

Furthermore, only one study comparing the effects of the two compounds on rCBF in healthy adults has been conducted. Studies focused on the compared effects of MPH and ATX on the dopaminergic and noradrenergic systems in ADHD patients would be crucial to help clarify their mechanisms of action, and their compared effects on symptomatic improvement. The recruitment of medication-naïve patients is crucial in this case given the long-term effects of MPH administration in the striatal dopaminergic system, as reviewed in this chapter. Furthermore, the homogeneity of the samples is also essential to identify the abnormalities associated to ADHD. Therefore, PET studies comparing the effects of the two drugs are needed in healthy adults but also in well-defined large samples of ADHD patients, who should ideally be medication-naïve and free of comorbid disorders.

Thus, one of the main limitations to the field is the lack of adequate NET radioligands. However, other aspects need also to be considered, such as the fact that changes in DA and NE systems do not happen in isolation in the brain, but there are interactions between the different neurotransmitter systems.

Therefore, at present, suitable techniques to study the compared effects of MPH or ATX on cortical regions are either the use of single-cell recordings in animals as recently done by Gamo et al (Gamo et al., 2010) or studies on blood flow in humans as recently conducted by Marquand et al (Marquand et al., 2012), which furthermore allow for the study of the effects on subcortical structures, known to be crucial in the brain dysfunctions presented by ADHD patients. PET is the best method to study the compared effects of drugs when the focus of the study is on drug-related changes on neurotransmitter systems, either by using radioligands that bind to the reuptake transporter or to neurotransmitter receptors. It is also the best method to use when the main focus of the study is on drug-related changes on blood flow at rest, although other techniques such as fMRI arterial spin-labelling can also be used, as shown by Marquand et al (Marquand et al., 2012). However this method can not be used in children.

Both PET and fMRI are adequate techniques when the focus of the study is on drug-related effects on brain activation during cognitive tasks. This is particularly relevant in children with ADHD, since PET cannot be used in children for ethical reasons, as it requires the injection of a radioactive substance into the blood stream.

Furthermore, fMRI and PET allow for the study of brain function in networks including both cortical and subcortical structures which, as reviewed in previous chapters, underlie the cognitive deficits presented by children with ADHD.

In this study, fMRI was used as it is the most adequate of the available techniques to be used in children with ADHD. The use of fMRI thus allows for the detection of dysfunctions in cognitive networks in patients when under placebo during cognitive tasks, and the changes in those in networks after administration of a single dose challenge of MPH and ATX in children with ADHD.

CHAPTER 4. EFFECTS OF MPH AND ATX ON COGNITIVE FUNCTIONS, BRAIN STRUCTURE AND FUNCION

MPH and ATX have shown to be safe and effective treatments for the symptoms of ADHD, both in children and adults (Hanwella et al., 2011; Hazell et al., 2010). In the case of MPH, the beneficial effects on behaviour are observable within hours whereas the effects of ATX are typically observable only after 4-6 weeks (Greenhill et al., 2001; Montoya et al., 2009; Swanson & Volkow, 2002).

Studies have focused not only on their efficacy as measured by behavioural function but also on the effects on cognitive functions. The number of studies on the effects of MPH and ATX on cognitive and brain function in children with ADHD is related to the time each medication has been prescribed for the disorder. Thus, as reviewed in the previous chapter, MPH has been used for decades for the treatment of ADHD and there is a substantial body of evidence about its effects on cognitive functions. Conversely, ATX has only been marketed and approved for the use in ADHD patients during the last decade, hence the comparatively reduced number of studies about its cognitive effects. However, the fact that MPH has consistently been the first-line treatment for decades does not mean that its mechanisms of action are well described: far from that, they are not yet known.

As reviewed in the previous chapter, MPH has dopaminergic effects in the striatum and it enhances both DA and NE in prefrontal regions. However, a recent study has provided evidence that its therapeutic effects are not only mediated by the dopaminergic but also noradrenergic system, as it has been shown to block norepinephrine transporters (NET) in other regions (Hannestad et al., 2010). ATX on the other hand is a more selective presynaptic NET blocker that has shown to block the NET almost completely in NET-rich areas including the LC, raphe nuclei and hypothalamus, and more moderately in the thalamus and subthalamic nuclei (Hannestad et al., 2010). However, their compared effects on cognitive functions in ADHD have not yet been studied. This chapter will review the available evidence of the effects of both drugs from neuropsychological and functional imaging studies. It should be noted that given the reduced number of studies on the effects of ATX, this review includes the effects of ATX reported in adult patients as well as in healthy subjects.

4.1 Effects on cognitive tasks

The effects of MPH have been studied across a number of cognitive functions, largely on cognitive control but also on attention, inhibition, reward or temporal processing. As reviewed in Chapter 1, children with ADHD have shown consistent deficits during sustained attention, temporal processing and WM; however, the most consistent evidence is that of deficits during motor response inhibition tasks (Willcutt et al., 2005). This, together with symptomatic improvement in hyperactive and impulsive behaviours after MPH administration, has led to the majority of neuropsychological studies on the cognitive effects of MPH in ADHD patients focussing upon on its effects during inhibitory functions (for reviews, see Chamberlain et al., 2011; Pietrzak, Mollica, Maruff, & Snyder, 2006; Swanson, Baler, & Volkow, 2010). Although the evidence on the effects of ATX is more limited, recently several studies on the effects of ATX on inhibition in children with ADHD have also been conducted.

However, before proceeding to the review of the literature, it is of note that many of the studies included subjects with a previous history of stimulant medication. Many studies compared the performance of children with ADHD when on MPH to that reported when they are off-MPH (or on placebo) after a washout period to ensure performance is not affected by previous MPH intake. However, this introduces a significant confound as there is evidence of the long-term effects of persistent stimulant administration both on brain activation and brain structure (Frodal & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009). Thus, this review will emphasize those studies where medication-naïve children with ADHD have been recruited, both during neuropsychological and imaging studies.

This chapter will review in detail the effects of MPH and ATX on inhibition, WM and temporal processing, as these are the aspects where children with ADHD have shown most consistent deficits, and constitute the focus of this PhD. The effects of MPH and ATX on other cognitive tasks will only be succinctly summarised at the end of this section.

4.1.1. Effect on inhibition tasks

4.1.1.1. Methylphenidate

The evidence is relatively consistent with regards to the enhanced inhibitory functions, in particular motor response inhibition, after MPH administration in ADHD patients. MPH has shown to improve performance of children (DeVito et al., 2009; Lijffijt et al., 2006; Schachar et al., 2008; Scheres et al., 2003) and adults with ADHD (Overtoom et al., 2009) during motor inhibition tasks both after a single dose (DeVito et al., 2009; Lijffijt et al., 2006; Overtoom et al., 2009) and repeated/chronic (Coghill, Rhodes, & Matthews, 2007; Schachar et al., 2008; Scheres et al., 2003) administration.

Using the SST, and compared to healthy controls, a single dose challenge of MPH normalised the deficits observed in previously medicated children with ADHD under placebo in the main inhibitory index, SSRT, coupled with relatively slower RT (DeVito et al., 2009). However, most of the studies have compared the performance within ADHD patients to their own performance without medication (either off-MPH or under placebo). Thus, shortened SSRTs, have also been described in children with ADHD under MPH when compared to the off-medication or placebo condition, whether they were previously medicated (DeVito et al., 2009; Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004; Lijffijt et al., 2006; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock, Schachar, & Logan, 1995) or, most importantly, medication-naïve children (Bedard et al., 2003; Scheres et al., 2003) and adults with ADHD (Overtoom et al., 2009), as well as a reduced number of commission errors (Lijffijt et al., 2006).

A single dose of MPH has also shown an effect on other performance measures that are not related to inhibitory processes during motor inhibition tasks. Thus, compared to placebo or off-MPH conditions, previously medicated children with ADHD under MPH have shown reduced MRT (Lijffijt et al., 2006; Tannock et al., 1989), intra-individual SD of RT (DeVito et al., 2009; Lijffijt et al., 2006; Tannock et al., 1989) and reduced number of omission errors (Lijffijt et al., 2006; Tannock et al., 1989). This was also observed in medication-naïve children with ADHD, where a single dose MPH challenge reduced MRT and SD of RT (Bedard et al., 2003).

Although there are fewer studies on the effects of prolonged MPH administration, similar findings have been reported, with improved inhibitory function after 1 week of treatment with MPH (Schachar et al., 2008), reducing typically longer MRTs both in previously medicated (Schachar et al., 2008) and medication-naïve children (Coghill et al., 2007; van der Meere, Shalev, Borger, & Wiersema, 2009), and reducing during GNG tasks the number of commission errors (Coghill et al., 2007), and intra-individual SD of RT (after 4 weeks of treatment) (Epstein, Brinkman, et al., 2011). However, some negative results have also been reported. Thus, 4 weeks of treatment with MPH in medication-naïve children with ADHD showed no effect on SSRT or MRT (Epstein, Brinkman, et al., 2011).

However, aside from the findings reported by Coghill et al (Coghill et al., 2007), results seem to be less positive for the GNG task compared with those reported in studies using the SST. A single dose challenge of MPH in medication-naïve children with ADHD showed no effect on performance during a GNG task (Rhodes, Coghill, & Matthews, 2006). In a recent study using incentivised and non-incentivised version of the GNG task, medication-naïve children with ADHD under placebo showed shorter RT when incentive was present compared to when it was not, however, the difference in RT between incentivised and non-incentivised disappeared after 4-weeks of treatment with MPH (Epstein, Brinkman, et al., 2011). MPH furthermore shortened SD of RT for both versions of the task and increased percentage of accuracy in the GNG task (independently of incentive) (Epstein, Brinkman, et al., 2011). After 4 weeks of MPH treatment, medication-naïve children with ADHD were tested under MPH and placebo during a GNG task, and depending on the characteristics of the task differential effects of MPH were observed: with short Inter-Stimuli Intervals (ISIs), performance was worse under MPH than under placebo, with more commission errors, but with long ISIs they made less commission errors under MPH than under placebo. According to the authors, these results suggest MPH worsens performance in a task where children with ADHD have previously done well (van der Meere et al., 2009).

Thus, the results during different motor response inhibition tasks suggest that either the SST is a more sensitive paradigm to detect the beneficial effects of MPH on this cognitive function, or that MPH has specific effects on different aspects of motor response inhibition processes. The SSRT is a measure of the speed of the motor inhibition process that differs from the percentage of commission errors, which is

typically taken as the main inhibitory measure in GNG tasks. Furthermore, it may be that MPH improves motor response inhibition of those responses that have already been triggered by the stimuli, as happens during the SST, and has less significant effect on the inhibition of a prepotent response which has not started by the time the NoGo stimuli is presented, as happens in the GNG task (Eagle et al., 2008; Rubia, Russell, et al., 2001). On the other hand, as suggested by some authors (Bedard et al., 2003; Tannock et al., 1989; Tannock, Schachar, et al., 1995), MPH may improve performance during inhibitory tasks not by affecting inhibitory function per se but by improving other processes, in particular motor response execution, as it consistently reduces MRT and SD of MRT in this task. This could affect the SSRT since it is dependent on the MRT, which is also reduced by MPH.

MPH seem to have therefore a positive effect on the speed of inhibitory processes as measured by the SSRT, as well as improved motor execution as measured by the shortened MRT and SD of RT although these effects seem to be mostly observed in previously medicated patients.

Less consistent is the evidence with regards to the effects of MPH administration during **interference inhibition** tasks.

Compared to the off-MPH condition, a single dose MPH challenge in previously medicated children with ADHD (but not in healthy children) has shown to improve interference inhibition during the Colour-Word Stroop task (Langleben et al., 2006), as well as during a modified version of the Stroop task (Brackenridge, McKenzie, Murray, & Quigley, 2011) and a Flanker task (Tucha et al., 2006). Similarly, repeated MPH administration in medication-naïve children with ADHD showed to improve accuracy and SD of RT during interference inhibition in children with ADHD (Epstein, Brinkman, et al., 2011). However, children with ADHD under a single dose of MPH compared to placebo showed no effect on interference inhibition conditions during Stroop or Eriksen Flanker tasks, both in medication-naïve (Bedard, Ickowicz, & Tannock, 2002; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Scheres et al., 2003), or previously medicated children with ADHD (Jonkman et al., 1999), although it improved naming speed during the Stroop task (Bedard et al., 2002) and RT during a Flanker task (Ridderinkhof et al., 2005).

Other tasks involving inhibitory processes are **cognitive flexibility** tasks, like switching, change tasks or set-shifting tasks (also defined in Chapter 1). During these, MPH effects have also shown to be inconsistent. During change tasks (Tannock,

Schachar, et al., 1995) and switching tasks (Cepeda, Cepeda, & Kramer, 2000; Kramer, Cepeda, & Cepeda, 2001), previously medicated children with ADHD under a single dose challenge of MPH have shown improved accuracy and shortened RT during switching trials than when under placebo (Cepeda et al., 2000; Kramer et al., 2001; Tannock, Schachar, et al., 1995). Similarly, during set-shifting tasks like the ID/ED from the CANTAB battery (described in Chapter 1) previously medicated children with ADHD under a single dose of MPH, successfully passed more stages in the ED dimension than when unmedicated (Mehta, Goodyer, & Sahakian, 2004). The findings from studies in medication-naïve patients are more inconsistent. Reduced MRT and SD during a set-shifting task have been reported under a single dose of MPH compared to placebo in medication naïve children with ADHD (Gunther, Herpertz-Dahlmann, & Konrad, 2010). However, other authors have shown no effects of MPH during the ID/ED from the CANTAB battery in medication-naïve children with ADHD, either after a single dose (Rhodes et al., 2005) or chronic administration (Coghill et al., 2007).

4.1.1.2. Atomoxetine

The data about ATX effects on response inhibition are much more scarce. It is only very recently that studies about the effects of ATX in children with ADHD have been conducted. Only one study has so far been conducted in children with ADHD under prolonged ATX treatment during a motor response inhibition task. Four weeks of ATX treatment in previously medicated children with pure ADHD showed no effects, although children with ADHD and comorbid RD showed shorter SSRT than at baseline (de Jong et al., 2009). Given the limited evidence available, studies in adult patients and healthy subjects will also be reviewed, as these are the only indications available of the potential effect of ATX on different cognitive functions.

Thus, compared to their own performance under placebo, previously medicated adults with ADHD under a single dose of ATX showed shorter SSRT (Chamberlain et al., 2007). Healthy adults under a single dose ATX challenge have shown shorter SSRT without effects on MRT to Go responses when compared to adults under placebo or the selective serotonergic reuptake inhibitor citalopram (Chamberlain, Muller, Blackwell, Clark, et al., 2006), which suggests that ATX had an specific effect on the inhibitory function without affecting the motor response execution process. Interestingly, a recent placebo-controlled, crossover study in

healthy adults that compared the effects of single doses of MPH and ATX on motor response inhibition (Nandam et al., 2011) showed that only MPH compared to ATX, citalopram or placebo shortened SSRT and SD of RT, thus suggestive of improved motor response inhibition after a single dose challenge of MPH challenge but not of ATX (Nandam et al., 2011).

During **interference inhibition** tasks such as the Stroop task, 3 weeks of treatment with ATX in adults with ADHD showed to improve interference scores compared to those of a parallel group under placebo (Spencer et al., 1998). Similarly, 10 weeks of treatment with ATX in adults with ADHD improved interference inhibition, as measured by the colour-word score, although only for those cases with a low baseline performance (Faraone et al., 2005). Other inhibitory tasks have been used to assess the effects of prolonged administration of ATX on medication-naïve children with ADHD. Thus, 4 weeks of treatment with ATX reduced the number of errors during set-shifting tasks, which was still observed at 12 weeks of treatment (Gau & Shang, 2010b).

4.1.1.3 Summary

The available evidence therefore supports the positive effect of MPH on inhibitory functions, with the most consistent findings supporting the positive impact of MPH administration on motor response inhibition, as measured by the SSRT in the SST. However, evidence is also suggestive of improvement in MRT and the reduced SD of MRT not only in the SST but also during cognitive inhibition and interference inhibition tasks, which has led some authors to suggest that MPH may have an effect on other processes underlying the task, such as motor response execution (Bedard et al., 2003; Tannock et al., 1989; Tannock, Schachar, et al., 1995). On the other hand, the few existing studies on the effects of ATX in ADHD patients (children and adults) provide evidence of its positive effects on motor response inhibition as measured by the SSRT. In opposition to this, the findings from the only study that has compared the effect of both compounds during motor response inhibition in healthy adults are intriguing, as the authors reported marked positive effects under MPH but not under ATX (Nandam et al., 2011). This highlights the need for comparison studies to observe the shared and differential effects of both compounds in ADHD patients.

However, the effects of MPH appear to be restricted to motor response inhibition tasks, as findings are not so consistent in other cognitive control tasks, such

as interference inhibition, change or set-shifting tasks. ATX has shown positive effects on interference inhibition, but the number of conducted studies is still very small.

The inclusion of previously medicated subjects in studies of single dose challenges of MPH or ATX cannot be understated as one of the most significant confounds in neuropsychological and functional imaging studies in ADHD, and this acquires potentially utmost relevance when we attempt to disentangle the effects of MPH and ATX on cognitive function and brain activation during cognitive tasks, as MPH has shown to have an effect on brain structure (Frodol & Skokauskas, 2012; Nakao et al., 2011) and brain function (Konrad et al., 2007). For this reason, those findings from studies recruiting pure medication-naïve samples (Bedard et al., 2003; Coghill et al., 2007; Epstein, Brinkman, et al., 2011; Rhodes et al., 2006; Scheres et al., 2003) are particularly relevant.

Furthermore, these studies suffer from the same limitations as previously reviewed in Chapter 1: many of them have included both males and females (Bedard et al., 2003; Bedard et al., 2002; Brackenridge et al., 2011; Epstein, Brinkman, et al., 2011; Jonkman et al., 1999; Konrad et al., 2004; Lijffijt et al., 2006; Schachar et al., 2008; Tannock et al., 1989; van der Meere et al., 2009), patients with comorbid conditions (Bedard et al., 2003; Bedard et al., 2002; Konrad et al., 2004; Lijffijt et al., 2006; Scheres et al., 2003; Tannock et al., 1989) or different subtypes of the disorder (Bedard et al., 2003; Bedard et al., 2002; Epstein, Brinkman, et al., 2011; Konrad et al., 2004; Lijffijt et al., 2006; Scheres et al., 2003) that will increase the heterogeneity of the sample, typically small per se (Jonkman et al., 1999; Lijffijt et al., 2006; Tannock et al., 1989), and therefore reduce the possibility of providing the field with replicable and consistent evidence.

4.1.2. Effects on attention tasks

4.1.2.1. Methylphenidate

An early meta-analytic review of studies using sustained attention measures such as the Continuous Performance Test (CPT) (Losier et al., 1996) showed that MPH administration compared to placebo significantly improved the number of omission errors and, to a lesser extent the number of commission errors (Losier et al., 1996). This has also been shown in later studies. Thus, in previously medicated

children with ADHD, single doses of MPH reduced the number of omissions errors (Hanisch, Konrad, Gunther, & Herpertz-Dahlmann, 2004; Konrad et al., 2004; Spencer et al., 2009; Teicher, Lowen, Polcari, Foley, & McGreenery, 2004; Tucha et al., 2006), commission errors (Huang, Chao, Wu, Chen, & Chen, 2007; Rosa-Neto et al., 2005; Spencer et al., 2009; Teicher et al., 2004), latency of responses and SD of RT (Huang et al., 2007; Konrad et al., 2004; Rosa-Neto et al., 2005; Spencer et al., 2009; Teicher et al., 2004). Importantly, reduced numbers of omission, commission errors and variability of responses have been reported also in medication-naïve children with ADHD after single dose MPH challenge (Gunther et al., 2010).

Positive effects have also been reported after repeated administration of MPH. Thus, 1-week of treatment reduced the number of omission errors in previously medicated children with ADHD (Schachar et al., 2008). Six-weeks of treatment with MPH reduced the number of commission errors and variability of responses in medication-naïve children with ADHD (Johnson, Barry, et al., 2008). Similarly, after 1 year of treatment with MPH reduced commission errors were reported in children with ADHD (Aggarwal & Lillystone, 2000).

Some normalising effects have also been reported for MPH during sustained attention tasks. A single dose MPH challenge in previously medicated children with ADHD normalised the deficits observed when they were under placebo relative to healthy participants for time on task and attention shifts (Teicher et al., 2004), and in the SD of RT during a vigilance task (Tucha et al., 2006). Six-weeks of treatment with MPH reduced and normalised the enhanced number of commission errors observed in medication-naïve children with ADHD under placebo as compared to healthy controls during the Sustained Attention to Response task (SART, defined in Chapter 1), and also reduced fast moment to moment variability of responses (Johnson, Barry, et al., 2008).

During other attention tasks single doses of MPH have also shown to have a positive effect in children with ADHD. Thus, compared to the placebo condition, a single dose MPH challenge in previously medicated children with ADHD has shown to reduce intra-individual SD during alerting and focused attention (Konrad et al., 2004), MRT, omission and commission errors during focused and divided attention tasks (Konrad et al., 2004; Tucha et al., 2006). However, no effects have been reported during alertness (Tucha et al., 2006).

4.1.2.2. Atomoxetine

Very little evidence is available with regards to ATX. Prolonged ATX administration in medication-naïve children with ADHD has shown to reduce latency of responses and omission errors, after both 4 and 12 weeks of treatment (Gau & Shang, 2010b). Similarly, a single dose of ATX administration reduced the number of commission errors during a sustained attention task in previously medicated adults with ADHD (Chamberlain et al., 2007).

4.1.2.3. Summary

The evidence provides support for the positive effects of MPH on sustained attention tasks, as well as preliminarily also for ATX. Unfortunately, the evidence from studies recruiting medication-naïve patients is very limited (Gau & Shang, 2010b; Gunther et al., 2010; Johnson, Barry, et al., 2008). It is interesting that there seem to be no clear indicator of which is the most sensitive measure of the effects on attention by MPH on these tasks whether omission errors or commission errors. Whether MPH improves performance during sustained attention tasks due to reduced impulsiveness, to improved efficiency of attention processes or both is still therefore to be elucidated.

4.1.3. Effect on WM tasks

4.1.3.1. Methylphenidate

Different effects have been reported during WM tasks, depending on the type of WM paradigms used. The most consistent evidence is for improved performance during visuo-spatial WM tasks, as will be reviewed below.

A single dose MPH challenge in children with ADHD has shown to improve performance during visuo-spatial WM tasks: previously medicated children with ADHD under MPH compared to their own performance under placebo have shown a reduced number of errors (Mehta et al., 2004), and improved storage and spatial manipulation (McInnes, Bedard, Hogg-Johnson, & Tannock, 2007). Studies on medication naïve samples have also reported some positive results, with single dose challenges of MPH improving accuracy (Bedard, Martinussen, Ickowicz, & Tannock, 2004), storage and spatial manipulation (Bedard & Tannock, 2008). However, a lack of effects of MPH on visuo-spatial WM tasks has also been reported, both in

medication-naïve samples after a single dose (Rhodes et al., 2006) or prolonged MPH administration (Coghill et al., 2007), as well as in previously medicated children with ADHD compared to placebo, although in this case there was an increased latency of responses (Tannock et al., 1989).

Some studies have compared parallel groups, that is, a group of healthy controls, a group of medication-naïve or unmedicated children with ADHD and a third group of medicated children with ADHD. In these studies, medication-naïve children with ADHD compared to healthy controls showed a reduced number of errors than children with ADHD who were under their usual dose of MPH, whose performance did not differ from that of healthy control children (Barnett et al., 2001; Kempton et al., 1999; Vance, Maruff, & Barnett, 2003).

The few studies that have focused on verbal-auditory WM tasks have shown inconsistent results, with a single dose MPH challenge in previously medicated children with ADHD showing no effects when compared to their own performance under placebo (McInnes et al., 2007). Similarly, a recent study using a verbal N-Back task showed no effects of prolonged MPH administration in medication-naïve children with ADHD (Epstein, Brinkman, et al., 2011). However, a single dose of MPH at medium dose (0.45 mg/kg) in medication-naïve children with ADHD improved their performance on the manipulation component of a verbal-auditory WM task compared to placebo (Bedard & Tannock, 2008).

4.1.3.2. Atomoxetine

Studies using WM tasks with ATX are scarce and results are inconsistent. Previously medicated adults with ADHD under placebo were less accurate than healthy controls in a visuo-spatial WM task, which persisted after ATX challenge (Chamberlain et al., 2007). However, these adults showed improved strategy utilization (Chamberlain et al., 2007), which has also been recently reported after repeated ATX administration in medication-naïve children with ADHD during a visuo-spatial WM task, although this was observed after 12 weeks of treatment rather than 4 weeks of treatment (Gau & Shang, 2010b). However, another study showed that after 4 weeks of treatment with ADHD, previously medicated children with ADHD improved performance (normalisation of deficits observed under placebo compared to controls) in a visuo-spatial WM task only in those cases with comorbid reading disorder but not in children with pure ADHD (de Jong et al., 2009).

4.1.3.3. Summary

Thus, there is some evidence for the positive effects of both compounds on visuo-spatial WM processes. However, given the relevance of the role of verbal-auditory WM during academic and daily life (Gathercole & Alloway, 2006), the potential impact of the treatments routinely prescribed for the disorder seems understudied.

4.1.4. Effects on temporal processing tasks

4.1.4.1. Methylphenidate

The evidence of the effects of MPH on temporal processing tasks is scarce, and non-existent in the case of ATX. In previously medicated children with ADHD, single doses of MPH compared to the off-MPH or placebo condition have shown to improve sub-seconds synchronization (Ben-Pazi, Shalev, Gross-Tsur, & Bergman, 2006), and to reduce their variability of responses during a time production task (without effects on accuracy or MRT) (Baldwin et al., 2004).

A single dose MPH challenge in medication-naïve children with ADHD showed no effect on performance during sensorimotor anticipation, synchronization and a TD task of seconds (Rubia, Noorloos, et al., 2003). On the other hand, prolonged MPH administration in medication-naïve children during 4 weeks has been associated with reduced variability and increased speed of responses during sensorimotor synchronization and a reduction in variability and impulsive errors in an anticipation task (Rubia, Noorloos, et al., 2003). However, 4-weeks of treatment with MPH showed no effects on their performance during a TD task of seconds (Rubia, Noorloos, et al., 2003). Similarly, 4-weeks of treatment with MPH (with a different condition each week: either placebo or 5, 10, 15 mg of MPH) showed no effects on the performance of children with ADHD during a time reproduction task (Barkley, Koplowitz, Anderson, & McMurray, 1997).

During temporal discounting tasks measuring temporal foresight, previously medicated children with ADHD after a single dose of MPH relative to their own performance under placebo have shown a reduced delay discounting rate during an experiential discounting task but not when the discounting task was hypothetical (Shiels et al., 2009).

4.1.4.2. Atomoxetine

So far, however, there are no studies that have examined the effects of ATX on temporal processes, either in patients with ADHD (neither children nor adults) or healthy subjects.

4.1.4.3. Summary

Thus, the reduced number of studies on the effects of MPH on temporal processing functions supports a positive impact of the drug during sensorimotor synchronization. The evidence in healthy subjects suggest that time perception is mediated by dopaminergic networks (Rubia et al., 2006; Wiener et al., 2010) and it can therefore be expected that stimulant medications would enhance time perception processing. Thus, given the limited evidence on the effects of MPH in patients with ADHD, more studies are needed on this field.

4.1.5. Effects of MPH and ATX on other cognitive functions

Some studies have also shown the effects of MPH on cognitive tasks in children with ADHD, with mounting evidence for positive effects during rewarded tasks. Thus, previously medicated children with ADHD have shown improved performance under a single dose of MPH than under placebo in a rewarded sensorimotor task that required progressively increased button-pressings to receive the rewards (Wilkison, Kircher, McMahon, & Sloane, 1995). Children with ADHD showed improved performance during motor response inhibition and visual attention tasks which involve contingencies manipulations (reward and response cost) under a single dose of MPH than under placebo (Tamm & Carlson, 2007). Similarly, other studies had shown improved performance in children with ADHD under stimulant medication compared to placebo during a rewarded signal detection task (Tripp & Alsop, 1999). During a gambling task, previously medicated children under a single dose of MPH have shown to make more conservative bets than when under placebo (DeVito et al., 2008).

4.1.6. Dose-related effects of Methylphenidate

Some studies have furthermore studied the potential association between different doses of MPH and performance improvement in ADHD. Typically, studies

on the effects of a single dose of MPH have used either two or three different dosages with low (0.25-0.30 mg/kg), medium (0.45-0.6 mg/kg) and high dosages (0.9-1 mg/kg). Although some studies report no differences between the different doses used (Bedard et al., 2002; Scheres et al., 2003; Shiels et al., 2009; Tannock, Ickowicz, & Schachar, 1995), the findings from those that report an effect suggest that these may be task-dependent. Thus, linear effects with more pronounced improvements at higher doses have been reported during fast trials in WM (Tannock, Ickowicz, et al., 1995), change-RT (Tannock, Schachar, et al., 1995) and attention tasks (Gunther et al., 2010; Konrad et al., 2004). Also linear effects were found for MRT and SD of RT (Spencer et al., 2009) or in MRT during inhibition processes (Ridderinkhof et al., 2005; Tannock et al., 1989), as well as in SSRT during inhibitory tasks (Lijffijt et al., 2006). However, an inverted-U effect has also been described for the SSRT during motor inhibition (Konrad et al., 2004), as well as during focused attention or variability of responses during sustained attention tasks (Gunther et al., 2010), and during auditory-verbal memory tasks (Bedard & Tannock, 2008). Another study using slightly lower doses (0.21, 0.31, 0.41 mg/kg) found a linear relationship with improvement in visuo-spatial and verbal-auditory WM tasks (McInnes et al., 2007). However, this could be due to the lower doses, and had they included a higher dose condition they may have found the inverted-U effect described by Bedard et al (Bedard & Tannock, 2008).

Similarly, a study on the effects of chronic MPH administration at fixed doses (0.3mg/kg, 0.6 mg/kg) showed very little differences between the effects of these, with only higher doses shortening RT during motor response inhibition tasks (Coghill et al., 2007).

Some of these dose-related effects may be affected by the inverted U-shape relationship between neurotransmitter levels and cognitive performance which varies depending on each cognitive function, as different levels of neurotransmitters may be necessary (Arnsten, 2009; Cools & D'Esposito, 2011; Gamo et al., 2010; Robbins, 2010). Fronto-striatal dopaminergic systems show a stability/flexibility trade-off in the brain (Cools & D'Esposito, 2011). Optimal levels of DA on PFC (via their action on D1 receptors) allow for the stability of representations withheld in WM by inhibiting neural firing to irrelevant stimuli (Arnsten & Pliszka, 2011; Cools & D'Esposito, 2011), while these levels seem to be too low to engage dopaminergic activity in the striatum via D2 receptors. However, with higher DA levels, D2 receptors stimulation in the striatum facilitates flexibility and rapid updating of

information (Cools & D'Esposito, 2011), while excessive D1 stimulation in the PFC suppresses firing both to relevant and irrelevant stimuli (Arnsten & Pliszka, 2011; Cools & D'Esposito, 2011).

4.1.7. Findings from neuropsychological studies: summary and conclusions

Most of the evidence on effects of MPH and ATX during neuropsychological studies supports the positive effects of MPH on inhibitory processes, in particular during motor response inhibition tasks, mostly when measured using the SST. There is consistent evidence for a shortened SSRT, suggestive of improved speed of the inhibitory function. However, the limited evidence for a reduction in the number of commission errors during motor response inhibition is intriguing and suggests that the effect of MPH is more on the speed of the inhibitory process rather than the likelihood to inhibit. This may be indicative of a higher sensitivity of the SSRT to detect the effects of MPH on motor response inhibition processes. There is some consistent evidence of effects on other measures of the task under single doses or chronic MPH administration like shortened MRT and reduced intrasubject SD of RT, suggesting that the effect is not specific to the inhibitory process but also motor execution processes. However, this evidence is mostly coming from studies that recruited previously medicated ADHD children. Nevertheless, this has led to the suggestion that MPH may not improve inhibitory processes per se, but may improve the speed of motor execution processes and the speed of the inhibitory process (Bedard et al., 2003; Tannock et al., 1989; Tannock, Schachar, et al., 1995).

On the other hand, with regards to ATX very little is known. Studies in both healthy adults and those with ADHD show that ATX administration shortens SSRT, indicative of improved inhibitory function, as well as improved interference inhibition (although only in those cases of impaired performance at baseline), and improved performance in change or set-shifting tasks in children with ADHD. The lack of effects on MRT of Go responses in these tasks, suggests that its effects are more specific on inhibitory processes without affecting motor response execution process, as opposed to the effects described for MPH.

However, contrary to this interpretation, a recent study comparing a single dose of ATX and MPH on healthy adults has shown that only MPH improved SSRT (Nandam et al., 2011), and in children with ADHD chronic ATX only improved SSRT in those cases with comorbid reading disorder (de Jong et al., 2009). Given the

very limited evidence available, more studies are needed to get more conclusive results about the exact nature of the effects of ATX on motor inhibition processes.

MPH also showed positive effects during sustained attention tasks, with reduced number of omission errors, commission errors, MRT, SD of RT and time on task. On the other hand, ATX has also shown some positive effects both in children and adults with ADHD, such as a reduced number of omission and commission errors and latency of responses. Nevertheless, given the reduced number of studies addressing these tasks, the findings can only be considered as preliminary and more research is needed.

During temporal processing paradigms, only studies of the effects of MPH exist. In this case, the evidence supports the positive effects on time processes, although not consistently, with mixed results. Whether this may be due to the design of the tasks, and whether the tasks are not sensitive enough to detect the effects of the drugs is something to consider.

During WM tasks the little evidence available seems to support the positive effect of MPH on visuo-spatial WM tasks, and not that clearly during verbal-auditory WM tasks. Single doses of ATX meanwhile have shown no effects on visuo-spatial WM tasks neither in adults with ADHD, nor in children with ADHD after 4 weeks of treatment. However, there is evidence of positive effects when the treatment is continued during 12 weeks. This results are in line with the time course shown for behavioural effects, as ATX has been reported to reach its maximum clinical efficacy only after 12 weeks of treatment (Montoya et al., 2009), and therefore may suggest that its beneficial effect on WM processes may only be observed after chronic administration.

Only few studies have tested the association between the reported effects of MPH on cognitive measures and symptomatic profile with, however, little success (Barnett et al., 2001; Mehta et al., 2004). Nevertheless, it needs to be highlighted that these studies suffer in their majority from the same limitations as those reviewed in chapter 1, when describing the evidence from neuropsychological studies in ADHD. These comprise the inclusion of small samples of subjects with different subtypes of ADHD, of males and females, or the presence of subjects with comorbid conditions, which increase the heterogeneity of the sample. Most importantly, as mentioned at the beginning of this chapter, the inclusion of subjects with a previous history of stimulant medication constitutes possibly the most significant confound in the studies

reviewed. These factors were extensively discussed in chapter 1, and therefore they will not be further discussed here.

Thus, additional evidence on the effects of ATX during different cognitive functions in ADHD patients is urgently needed. Furthermore, studies comparing the effects of both drugs in homogeneous samples would allow to elucidate the commonalities and differences of the cognitive effects of these drugs on medication-naïve children with ADHD.

Whether the observed improvements are associated with the presence of previous deficits in children with ADHD merits further discussion. Some of the studies have reported differential effects depending on the baseline performance levels, with significant improvements after medication in those cases with impaired baseline performance levels (Faraone et al., 2005; Hanisch et al., 2004). This is consistent with the results from other studies, reviewed in chapter 3, where responders to MPH behaviourally were those who presented with more severe abnormalities in the dopaminergic system at baseline (Krause et al., 2005; la Fougere et al., 2006). Furthermore, as reported in chapter 2, the evidence for the presence of abnormalities or deficits during interference inhibition tasks in children with ADHD is not as consistent as that for motor response inhibition processes. Thus, it is possible that MPH has stronger effects on those cases where the deficits both at the cognitive and catecholaminergic neurotransmitter systems levels are more pronounced, and there is therefore more room for improvement. However, some evidence in the opposite direction has also been provided, with larger improvements in those children with ADHD with better baseline performance (Mehta et al., 2004).

The effects of MPH and ATX should ideally be compared not only using a single cognitive function, but using a range of tasks loading on executive and non-executive cognitive functions, so as to provide more details on their compared effects on cognition. However, only few studies have used neuropsychological batteries to assess the effect of MPH or ATX on cognitive processes (Coghill et al., 2007; Gau & Shang, 2010b; Rhodes et al., 2006), and therefore more studies are needed. These studies would furthermore help to identify whether there are specific beneficial effects on specific cognitive functions for the drugs studied, which at present is unknown.

Furthermore, the doses required for positive behavioural effects may be higher than those for positive cognitive effects (Sprague & Sleator, 1977; Swanson et al., 2010). However, the majority of the studies have used a single dose, and therefore

more studies on the compared effects of different dosages both of MPH and ATX are needed.

Results from the MTA study showed a dissipation of the superior effects of stimulant treatment relative to other behavioural treatment options after approximately 3 years (for a review, see Swanson et al., 2010). How and whether this occurs also at a cognitive function level would merit further investigation, and whether this dissipation of effects long-term also occurs with ATX. Therefore, studies on the compared effects of a single dose and chronic administration of MPH and ATX are strongly needed.

4.2 Effects of MPH and ATX on brain structure and function

The study of the effects of MPH and ATX cannot be limited to the study of their effects on cognitive functions, but the neural underpinnings of these effects on cognition need to be clarified. Functional imaging studies on the effects of the different medications during cognitive tasks not only provide this evidence, but also help to increase our knowledge about the mechanisms of action underlying the observed cognitive changes.

4.2.1. Indirect evidence for the effects of MPH on brain development/structure

At present, there is not a single prospective longitudinal imaging study within randomised clinical trials with a focus on the effects of MPH on brain structure, and only indirect evidence of its potential effects from small studies conducting mostly cross-sectional comparisons between medicated and unmedicated groups of children with ADHD is available. Thus, given the severe limitations of most of the existent studies, the evidence will be succinctly summarised here. This is only applicable to MPH, as there are no such studies for ATX as yet.

Only one longitudinal study has so far focused on the effects of MPH on brain structure in a very small subgroup of children of their original sample. This study showed that those children who had received long-term psychostimulants during a 4-years period (N=24) had more normal cortical thickness in the right precentral gyrus, left middle/inferior frontal gyrus and in right parieto-occipital regions, due to a more rapid cortical thinning rate in the non-medicated group (N=19) (Shaw, Sharp, et al., 2009).

A longitudinal study conducted a cross-sectional post-hoc comparison between medicated and unmedicated patients, as well as with healthy controls (Castellanos et al., 2002). The authors reported significantly reduced white matter volumes in unmedicated patients (N=49) compared to both long-term treated patients (N=103) and healthy controls (N=139) (Castellanos et al., 2002). However, the cross-sectional nature of the comparison and the reduced number of cases included in the post-doc comparison limit the interpretation of this finding.

In addition, some small-numbered cross-sectional studies found more normal structure in the posterior inferior vermis of the cerebellum and in right ACC volume compared to healthy controls in long-term medicated (Pliszka et al N=16; Bledsoe et al N=18) compared to unmedicated children with ADHD (Pliszka et al N=14; Bledsoe et al N=14), who had smaller volumes compared to healthy controls (Pliszka et al N=21; Bledsoe et al N=15) (Bledsoe et al., 2009; Pliszka, Lancaster, Liotti, & Semrud-Clikeman, 2006).

As reviewed in chapter 2, meta-analytic studies of findings from VBM studies in children with ADHD have shown that the most significant volumetric grey matter reductions are in the right basal ganglia (Frodl & Skokauskas, 2012; Nakao et al., 2011). Furthermore, those studies with a higher proportion of long-term medicated patients no longer showed striatal grey matter volumetric abnormalities (Frodl & Skokauskas, 2012; Nakao et al., 2011). Similarly, a cross-sectional study showed that children with ADHD presented with inwards deformations in the basal ganglia that were associated to ADHD symptom severity (Sobel et al., 2010). However, when their medication status was taken into account, the group not taking stimulant medication showed exacerbated inward deformations compared to controls, whereas the group taking long-term stimulant medication showed outwards deformations that attenuated the differences relative to the healthy control group (Sobel et al., 2010).

A limitation of all these studies is their cross-sectional nature, and the presence of a potential selection bias. To assess adequately the potential effects of stimulant medication on brain structure, prospective longitudinal imaging studies within randomised clinical trials are needed. However, all studies seem to be in the same direction and there is thus some indication that long-term stimulant-treated children may have more normal brain structure than untreated children, which could potentially point towards a protective effect of MPH. However, this needs to be confirmed in well-controlled longitudinal randomised longitudinal trials.

4.2.2. Effect on resting state

Some studies have tried to identify changes in cerebral blood flow (rCBF) during the resting state by using PET in ADHD patients. In this section, only the evidence for the effects of MPH on the dysfunctions reported during the resting state of patients will be succinctly summarised, as there is no such type of studies on the effects of ATX as yet.

Using fMRI relaxometry, 1-week of treatment with MPH has been shown to increase the function of the vermis of the cerebellum (Anderson, Polcari, Lowen, Renshaw, & Teicher, 2002). Furthermore, SPECT studies have shown the effect of MPH on rCBF both in medication naïve (Kim, Lee, Cho, & Lee, 2001; Lee et al., 2005) and in previously medicated patients (Langleben et al., 2002; Lou, Henriksen, Bruhn, & Borner, 1989; Szobot et al., 2003), using a single dose of MPH (Lou et al., 1989) or prolonged treatment (>1 week) (Kim et al., 2001; Lee et al., 2005; Szobot et al., 2008). Thus, MPH within children with ADHD upregulated rCBF in frontal regions (Kim et al., 2001), thalamus (Kim et al., 2001), striatum (Kim et al., 2001; Lou et al., 1989) and parietal cortices (Szobot et al., 2003) and decreased rCBF in sensorimotor regions (Lou et al., 1989). Also using SPECT, a single dose MPH challenge in previously medicated children with ADHD decreased rCBF in bilateral precentral (motor cortex) regions and the ACC compared to the off-medication condition (Langleben et al., 2002). Furthermore, MPH reduced the dysfunction in medication-naïve children with ADHD compared to healthy controls in frontal and occipital regions as well as in the striatum (Lee et al., 2005).

In adults with ADHD, similar improvements on the abnormal patterns of activation have been reported. Using PET, 3 weeks of treatment with MPH on previously medicated adult patients modulated baseline hyperactivity in precentral gyrus, caudate and claustrum, and increased activity (rCBF) in cerebellar vermis (Schweitzer et al., 2003). When compared to the off-medication condition, adults with ADHD under their usual stimulant medication showed a decrease in perfusion in the left caudate, IFC, parietal cortices and parahippocampal gyrus (O'Gorman et al., 2008). On the other hand, there are also studies where negative results have been reported. Thus, a single dose (Matochik et al., 1993) or chronic (Matochik et al., 1994) treatment with stimulant medication (methylphenidate and d-amphetamine) in adults with ADHD showed no effects on global glucose metabolism.

Thus, the evidence in children and adults with ADHD show mixed results. While in children with ADHD MPH has shown to have mostly enhancing effects on rCBF in predominantly frontal and subcortical regions, in adults with ADHD MPH treatment had either no effect or downregulated rCBF, with the only exception of Schweitzer et al (Schweitzer et al., 2003) who additionally reports enhanced rCBF in the cerebellum. Whether this is due to long-term adaptive responses of the brain to the dysfunctions they present with throughout their lives or a response to chronic MPH treatment can only be elucidated with long-term longitudinal randomised clinical studies.

There is some evidence of brain activation patterns in non-responder patients that suggests that clinical response to MPH may happen only when there is room for improvement on brain function. Thus, those subjects who did not respond to MPH had higher baseline rCBF in midbrain, posterior cerebellum and middle frontal gyrus (Schweitzer et al., 2003) and ACC, claustrum and putamen (Cho et al., 2007), as well as reduced rCBF in the parietal lobe (Cho et al., 2007). However, given the small sample sizes and heterogeneity of the samples further studies are needed to clarify this aspect.

4.2.3. PET studies during cognitive tasks

Some evidence from PET studies in healthy adults during cognitive tasks suggests increased efficiency of the neuronal networks after a single dose of MPH. In adults with ADHD, 3-weeks of treatment with MPH enhanced activation during a WM task under MPH compared to the unmedicated condition in the right thalamus and precentral gyrus (Schweitzer et al., 2004). Furthermore, there were no normalising effects when compared to healthy controls, as the reduced rCBF in left IFC, STG and ACC, and the enhanced activation in basal ganglia and cerebellum observed when unmedicated were not normalised after MPH. However, performance in the task was improved, with a reduction in MRT within patients, and a normalisation of the reduced accuracy observed when off-MPH compared to healthy subjects (Schweitzer et al., 2004).

In healthy subjects, blunted metabolic responses or reduced rCBF, suggestive of increased neural efficiency, have been reported in medial frontal and temporo-parietal regions together with increased rCBF in cerebellum compared to placebo during a mathematical cognitive task (20 mg, orally)(Volkow et al., 2008), working

memory (40 mg, orally)(Mehta et al., 2000) or sustained attention tasks (0.25 mg/kg, i.p.) (Udo de Haes, Maguire, Jager, Paans, & den Boer, 2007). The findings are less consistent on other regions, with rCBF in the cingulate being increased (Udo de Haes et al., 2007) or decreased (Volkow et al., 2008) after MPH administration compared to placebo during sustained attention and mathematical cognitive tasks, respectively. This suggests the presence of context-dependent effects of MPH, in line with previous evidence of increased saliency of stimuli after MPH administration (Volkow, Wang, Fowler, Logan, Jayne, et al., 2002; Volkow et al., 2004).

4.2.4. Effect on brain function during inhibitory tasks

Given the key role of the striatum in inhibitory processes, these have been typically considered as dopaminergically innervated. However, there is evidence supporting the positive effects on inhibitory processes of predominantly noradrenergic drugs, like ATX both in animal studies (Bari, Eagle, Mar, Robinson, & Robbins, 2009; Eagle et al., 2008) and in neuropsychological studies in humans as reviewed in section 4.1. It seems therefore plausible that both drugs have an enhancing effect in PFC activation during inhibitory processes, since in Chapter 3 it has been reviewed that both MPH and ATX enhanced the levels of both catecholamines in this region (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006), and that only MPH will have an effect on the striatum (Berridge et al., 2006; Bymaster et al., 2002; Koda et al., 2010; Swanson et al., 2006; Volkow, Wang, Fowler, Gatley, et al., 1998; Volkow, Wang, Fowler, Logan, Franceschi, et al., 2002).

4.2.4.1. Methylphenidate

MPH enhances or normalises inhibitory performance in children with ADHD, as has been reviewed in a previous section of this chapter. Furthermore, performance improvements during inhibitory tasks in children with ADHD under MPH have been associated not only with enhanced activation in inhibition-related networks, but also with modulatory effects on other neural circuits.

During successful inhibitory trials in the SST, a single dose challenge of MPH in medication-naïve children with ADHD normalised the underactivation when under placebo compared to healthy controls in temporo-parietal cortices and cerebellum (Rubia, Halari, Mohammad, et al., 2011).

Similarly, during GNG tasks, a single dose MPH challenge in previously medicated children with ADHD has shown to enhance activation compared to a placebo (Epstein et al., 2007) or off-MPH conditions (Vaidya et al., 1998) in key inhibitory regions, including IFC and MFC, as well as striatal regions (Epstein et al., 2007; Vaidya et al., 1998). Further upregulating effects have been reported in the ACC, IPL and cerebellum (Epstein et al., 2007). Although patients showed an improved performance in the task, with shorter SD of RT and improved target stimulus discrimination, this was not associated to the changes in brain activation (Epstein et al., 2007).

During an incentivised GNG task, previously medicated children with ADHD showed reduced task-related deactivation in the DMN (including medial prefrontal cortex, PCC, inferior parietal and lateral temporal cortices) under the low incentive condition, which was normalised under a single dose MPH challenge (Liddle et al., 2010). The authors report reduced sensitivity (d') and enhanced omission errors in children with ADHD off-MPH, which disappeared under a single dose of MPH (Liddle et al., 2010).

A study used fNIRS (described in Chapter 2), finding enhanced activation in the right lateral prefrontal cortex during a Go/No Go task after a single dose MPH challenge in previously medicated children with ADHD compared to the off-MPH condition, which was associated with improved accuracy during NoGo trials (Monden et al., 2011).

Finally, in previously medicated children with ADHD during the motor response inhibitory trials of a modified version of the Flanker task which included a NoGo component, no effect of a single dose MPH challenge was observed (Lee, Han, Lee, & Choi, 2010).

There is also some evidence that MPH improves brain function associated with performance monitoring or error monitoring. In the only study conducted using the SST and recruiting a medication-naïve sample of children with ADHD, a single dose MPH challenge compared to placebo upregulated activation in left MFC, bilateral IFC and lenticular nucleus and right parietal regions only during failed inhibitory trials (Rubia, Halari, Mohammad, et al., 2011). These upregulation effects were furthermore associated with performance during the task, thus, enhanced activation in bilateral IFC was associated with longer post-error RT, the upregulation in right IFC was associated with longer MRT to go responses and the SD of RT was

associated with enhanced parietal activation. Also, when compared to healthy boys, children with ADHD under placebo showed underactivation in an error monitoring network involving left IFC, right dorsomedial prefrontal, pre-SMA, bilateral thalamus, PCC, temporo-parietal and occipital cortices (Rubia, Halari, Mohammad, et al., 2011), that was associated with post-error slowing (reduced at a trend level) in ADHD patients under placebo. When patients were under a single dose MPH challenge they no longer differed from healthy boys (Rubia, Halari, Mohammad, et al., 2011).

Other inhibitory tasks used to assess the effect of MPH during **interference inhibition** processes do not produce consistent findings. Using the Attention Network Test (ANT), in which one of the conditions is a variation of a Flanker task, Konrad et al (Konrad et al., 2007) observed that one year of treatment with MPH did not normalise the reduced function in the ACC in ADHD children compared to healthy children during interference inhibition processes.

Conversely, using a Simon task in a medication-naïve sample of children with ADHD, a single dose MPH challenge compared to the placebo condition enhanced activation in right IFC, premotor cortices, temporo-parietal lobes as well as in cerebellum, without significant effects on task performance (Rubia, Halari, Cubillo, et al., 2011). Furthermore, when compared to healthy boys, a single dose of MPH normalised the reduced function under placebo in left VMPFC and right IFC, as well as in basal ganglia and thalamus. However, MPH administration did not modify the underactivation observed in other key regions for conflict monitoring and interference suppression as the SMA, ACC and PCC and left temporo-occipital regions (Rubia, Halari, Cubillo, et al., 2011). The longer RT in ADHD under placebo compared to controls were furthermore not normalised by MPH.

Using a Stroop task, a single dose of MPH in previously medicated (responders) children with ADHD has shown to enhance activation in the control condition of the task in the ventral ACC and PCC, which according to the authors may represent the enhanced deactivation of the DMN during the condition of interest (interference inhibition) (Peterson et al., 2009). Furthermore, it was observed that the connectivity between left inferolateral prefrontal cortex and ventral ACC was also enhanced when under MPH compared to the off-MPH condition. However, this study did not have a placebo condition, and therefore cannot rule out the influence of subjects' expectations on the results.

Other studies have used modified versions of interference inhibitory paradigms. Thus, previously medicated children with ADHD were administered a single dose of MPH during a modified version of the Flanker task that included a component of motor response inhibition (no-go stimuli) (Lee et al., 2010). A single dose MPH challenge elongated MRT during incongruent trials and enhanced activation in right IFC, DLPFC, SFC and premotor regions (Lee et al., 2010).

During a emotional Stroop task, previously medicated children with ADHD off their daily medication compared to healthy controls showed greater reactivity in MFC to emotional stimuli, which was associated with greater levels of hyperactivity symptoms as measured by the Conners' Parent Rating Scale (at the time of their first scan) and normalised when on their usual dose of stimulant medication (Posner et al., 2011).

In a study using a parallel groups design in adults with ADHD, 6 weeks of treatment with MPH increased activation compared to that of a placebo group in the dorsal anterior midcingulate, DLPFC, premotor and parietal cortices, caudate, thalamus and cerebellum during interference inhibition, despite a lack of performance differences (Bush et al., 2008). Therefore, the evidence suggests beneficial effects of single dose MPH on brain activation during inhibition tasks which, as in neuropsychological studies, are more consistent for motor response inhibition than for interference inhibition tasks. MPH has shown to upregulate most consistently IFC and striatal regions in children with ADHD during tasks of motor and interference inhibition, with additional upregulating effects on temporo-parietal cortices.

4.2.4.2. Atomoxetine

Although no functional imaging study has focused so far on the effects of ATX during inhibitory processes in ADHD patients, two studies have tested healthy adults after a single dose of ATX compared to placebo using motor response inhibition tasks combined with fMRI. Both studies found upregulating effects in IFC as well as right STG, left anterior insula and SMA (Chamberlain et al., 2009; Graf et al., 2011). During response inhibition, a single dose of ATX enhanced activation (irrespective of their success in the inhibition trial) in the right IFC, extending to the superior temporal cortex and insula as well as improved motor response inhibition (shorter SSRT) (Chamberlain et al., 2009). Furthermore, the authors observed a positive association between plasma levels of ATX and activation in right IFC and

STG during successful inhibition trials only (Chamberlain et al., 2009). During a combined Eriksen Flanker and GNG task, healthy adults under a single dose of ATX administration showed enhanced activation during errors in incongruent NoGo trials in bilateral IFC extending to left insula, SMA and SFC/pre-SMA as well as increased number of errors during the incongruent No-Go trials (significantly associated to blood serum levels of ATX, but not with brain activation changes)(Graf et al., 2011). Phasic alertness is a noradrenergically regulated process which shows an inverted-U dose-response and may have had a detrimental effect on the performance of the participants during the cognitive task by enhancing NE levels to the right end of the curve (Aston-Jones & Cohen, 2005). In line with this, the authors furthermore report an increase in phasic alertness, which may underlie the accompanying enhanced number of commission errors in incongruent nogo trials (which were furthermore correlated with blood serum levels of the drug) (Graf et al., 2011).

There is only one study so far that, using eletrophysiological methods, has focused on the compared effects of repeated ATX and MPH administration in children with ADHD, using Event Related Potentials (ERP, defined in Chapter 2, section 2.1)(Kratz et al., 2012). Using a crossover design, the authors show that 8 weeks of treatment under each condition both equally improved MRT and errors during the conflict condition. In addition, both drugs reduced SD of RT, although MPH had significantly stronger effects than ATX. However, the ERPs associated to attention processes and stimulus evaluation (P3) did not differ from the reported at baseline, and only the Contingent Negative Variation (CNV), which is associated to anticipation and preparation, was significantly modulated only by MPH. The authors' interpretation of this finding is that only MPH improved brain function in relation to the preparation and allocation of attention resources. At the same time, changes in the CNV were positively associated to changes in SD of RT only under MPH and not under ATX (Kratz et al., 2012).

4.2.4.3. Summary

In conclusion, most studies report upregulating effects of MPH in children with ADHD on IFC, MFC and striatal regions, as well as improved downregulation in the DMN during inhibitory tasks (both GNG and Stroop). Furthermore, MPH has shown additional upregulating and normalising effects on motor execution and performance monitoring processes in IFC, striatal, pre-SMA and temporo-parietal

regions. On the other hand, there is no evidence for the effects of ATX on brain function during inhibitory processes in children or even adult ADHD patients. The only existing evidence from studies in healthy adults suggests enhancing effects of ATX in key regions during motor response inhibition tasks, most significantly the right IFC, as well as in other cortical regions including the right STG.

4.2.5. Effect on brain function during attention tasks

Attention tasks typically engage right lateralised networks including the IFC/DLPFC, pre-SMA, thalamus, the temporo-parietal junction and cerebellum (Lawrence et al., 2003; Tucker & Williamson, 1984).

4.2.5.1. Methylphenidate

The evidence on the effects of MPH or ATX on brain activation during attention functions is significantly more limited than that of inhibitory processes. Prolonged MPH administration in children with ADHD during reorienting attention processes did not normalise the underfunctioning temporo-parietal junction compared to healthy controls, but normalised the enhanced (potentially compensatory) activation at baseline relative to controls in insula and putamen (Konrad et al., 2007).

In a divided attention task, a single dose of MPH in previously medicated children with ADHD did not have any effect on performance and did not normalise the underactivation in right MTG, but showed some normalising effects on the underactivated baseline functioning of the left striatum compared to healthy controls (Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004). Furthermore, MPH enhanced activation in the basal ganglia both in children with ADHD and children with reading disorder during the divided attention task, which suggests that MPH has a general upregulating effect in the basal ganglia, independently of the presence of an attention disorder (Shafritz et al., 2004).

The only imaging study so far which has assessed the effects of MPH on sustained attention has shown that a single dose of MPH in medication-naïve children with ADHD enhanced activation in IFC, premotor cortex, PCC, precuneus and cerebellum, but only normalised the reduced functioning of temporo-parietal cortices. Enhanced activation compared to healthy boys was reported after MPH in DLPFC/IFC and right cerebellum. Omission errors, which were normalised under a single dose of MPH, were associated negatively with activation in right parietal

regions, and with the enhanced frontal and cerebellar activation, supporting thus the potential compensatory role of this enhanced activation (Rubia, Halari, Cubillo, et al., 2009). Finally, a single dose of MPH also normalised the underfunctional patterns of inter-regional connectivity in fronto-striatal, fronto-cerebellar, and cerebello-striatal intercorrelations, although cerebello-parietal connectivity deficits persisted (Rubia, Halari, Cubillo, et al., 2009). Thus, this study suggests that the effects of MPH on sustained attention functions may be stronger in normalising the abnormal connectivity within sustained attention networks rather than by normalising underfunctioning isolated regions.

4.2.5.2. Atomoxetine

No imaging studies have tested for the neurofunctional effect of ATX in ADHD patients or healthy subjects during attention tasks.

4.2.5.3. Summary

Thus, in children with ADHD the effects of MPH on attention networks seem to be task-dependent, with upregulating and normalising effects in frontal regions, basal ganglia, temporo-parietal cortices and cerebellum during sustained attention, but no effects on temporo-parietal dysfunction during focused and divided attention. Furthermore, during sustained attention tasks, a single dose of MPH in medication-naïve patients showed normalisation effects on most of the abnormal functional connectivity when under placebo relative to controls in fronto-striatal, fronto-cerebellar, and cerebello-striatal networks, and facilitated the engagement of potentially compensatory activation in cerebellar regions.

4.2.6. Effect on working memory tasks

As described in the previous chapters, WM is a higher cognitive process that involves the storage and manipulation of information, which typically engage the DLPFC and PL. Furthermore, it is known that WM is mediated by DA and NE in the PFC (Gamo et al., 2010), and that both drugs enhance the levels of both catecholamines in the PFC (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006). Therefore, it seems reasonable to expect both drugs to have enhancing and/or upregulating effects on PFC during WM tasks.

4.2.6.1. Methylphenidate

During a verbal-auditory WM task (N-Back), administration of their usual dose of MPH in previously treated children with ADHD improved their performance in the most difficult condition of the task (3-Back) compared to their own performance off-MPH, and normalised the performance deficits observed in the 2- and 3-Back when compared to controls. However, it showed no significant effect on brain activation compared to that observed when off-MPH (Kobe et al., 2009).

In a very small study including only 5 previously treated girls with ADHD, MPH compared to off-MPH improved accuracy in a visuo-spatial WM task (with data from only 4 of the participants) and reduced the enhanced brain activation in MFC as well as the functional connectivity between this region and basal ganglia (Sheridan, Hinshaw, & D'Esposito, 2010). The authors interpret these findings as a normalization of enhanced compensatory activation when off-MPH, given the cognitive demands on PFC during the task.

A single dose MPH challenge in previously medicated children with ADHD normalised the deficits observed when under placebo compared to healthy control children within IFC and MFC and improved the deficits observed in basal ganglia however, deficits in posterior temporo-occipital regions persisted (Prehn-Kristensen et al., 2011). The authors furthermore report improved and normalised the reduced accuracy when off-MPH compared to controls, although only in those trials when no distracters were present.

A recent study from Wong and Stevens (Wong & Stevens, 2012) showed the effects of a single dose MPH challenge in previously medicated children with ADHD during the Stenberg WM task. They report enhancing effects on activation and increased functional integration after MPH administration in the different WM networks identified, which involved most prominently (but were not limited to) left VLPFC, DLPFC and parietal network, as well as the ACC and PCC (Wong & Stevens, 2012). Although no significant effects on accuracy were reported, there was a shortened RT to targets, suggestive of decreased search time, with the highest effect at the lowest WM load. Furthermore, despite the lack of effects on accuracy, changes in functional connectivity patterns were linked to reductions in RT, with greater behavioural effects on the lowest WM load condition.

4.2.6.2. Atomoxetine

There are no studies investigating the effects of ATX on brain activation in ADHD patients during WM tasks. A recent study comparing the effects of single dose challenges of MPH and ATX on brain activation of healthy adults during WM processes using multivariate pattern recognition analyses showed that MPH had a stronger effect on upregulating task-relevant networks (bilateral DLPFC and IPL), while ATX had relatively stronger effects on the suppression of the DMN (medial PFC, PCC/Precuneus) (Marquand et al., 2011). However, these findings were highly context-dependent as they were only observed during the delay component of rewarded trials. This would be in line with studies from Volkow et al reviewed in the previous chapter (Volkow, Wang, Fowler, Logan, Jayne, et al., 2002; Volkow et al., 2004), which suggest that MPH seems to mimic the effect of reward on upregulating other cognitive processes, increasing the salience of stimuli.

4.2.6.3. Summary

In conclusion, the findings on WM tasks in children with ADHD seem to be relatively inconsistent, with some studies showing either no effects, downregulation of medial prefrontal regions or enhanced activation and functional integration of fronto-parietal WM networks. Whether this is due to the differences in the paradigms used, the previous medication history of the participants and/or the small sample sizes of the studies still need to be elucidated. The effects of ATX have only been studied in healthy adults, and ATX compared to MPH downregulated more strongly the DMN.

4.2.7. Effect on timing tasks

Time perception processes are known to be mediated by fronto-striatal networks (Rubia, 2006; Wiener et al., 2010). Furthermore, as reviewed in the previous chapter, time perception networks are sensitive to dopaminergic manipulations (Baldwin et al., 2004; Rubia, Noorloos, et al., 2003) and accordingly there is consistent evidence that shows time perception deficits in ADHD patients, as reviewed in chapters 1 and 2.

4.2.7.1. Methylphenidate

Only one functional imaging study has so far tested the effects of MPH on brain activation during these cognitive functions in ADHD patients. Under a single dose of MPH compared to when under placebo, medication-naïve children with ADHD showed enhanced activation in left orbital and IFC, and at a more lenient threshold, also in key temporal discrimination regions comprising the right DLPFC, ACC and cerebellum, despite no differences in performance (Rubia, Halari, Christakou, et al., 2009). Furthermore, compared to healthy controls, a single dose MPH challenge normalised all areas of underactivation reported under placebo in OFC cortex, caudate and ACC and the enhanced activation in predominantly temporo-occipital cortices observed when ADHD boys were under placebo (Rubia, Halari, Christakou, et al., 2009).

4.2.7.2. Atomoxetine

There are no studies as yet on the effect of ATX during timing tasks in ADHD or healthy subjects.

4.2.7.3. Summary

The limited available evidence has shown that a single dose of MPH in medication-naïve children with ADHD normalises and upregulates key regions for TD, including IFC, ACC, basal ganglia and cerebellum. Both ATX and MPH have shown to enhance extracellular levels of DA in PFC, consequently shared effects may be shown in this region. Therefore, it would be interesting to compare the effects of both compounds during a TD task.

4.2.8. Effects of MPH on other cognitive tasks

There is some evidence that single dose MPH administration has also positive effects on brain function during reward-related tasks in children with ADHD. Thus, as mentioned above, during an incentivised GNG task, a single dose MPH challenge normalised the reduced task-related deactivation in the DMN under low incentive condition in previously medicated children with ADHD (Liddle et al., 2010). Furthermore, during the rewarded trials of a sustained attention task, single dose MPH administration to medication-naïve children with ADHD showed upregulating effects within subjects in right VMPFC, ACC and caudate, and normalised the enhanced

activation under placebo relative to controls in OFC and temporal regions (Rubia, Halari, Cubillo, et al., 2009).

4.2.9. Findings from imaging studies: summary and conclusions

Neuropsychological and functional imaging studies have thus provided consistent evidence of the effects of MPH on different cognitive functions and their underlying neural underpinnings respectively. More recently, studies have focussed upon the effects of ATX, although the evidence is much more limited.

The findings from functional imaging studies show that MPH has effects on inhibitory networks, most consistently upregulating key frontal and striatal regions, as well as other regions, like the improved downregulation in the DMN during inhibitory tasks (both GNG and Stroop). Furthermore, MPH has been shown to have upregulating and normalising effect on performance monitoring networks including IFC (most prominently left lateralised), basal ganglia, pre-SMA, thalamus, posterior cingulate and temporo-parietal regions.

On the other hand, the lack of studies on the effects of ATX on brain activation in children with ADHD during inhibitory tasks makes the comparison of the effects impossible. However, results are promising for ATX as well, as enhancing effects have been reported in healthy adults in the key inhibitory region, the right IFC, as well as in other cortical regions including the right superior temporal gyrus. Furthermore, enhanced activation in bilateral IFC and SMA, part of the performance monitoring network, have been reported during a mixed GNG/Flanker task. It is likely that both drugs share effects on prefrontal regions, given that both enhance DA and NE levels in prefrontal areas. However, how their effects will compare in ADHD patients in the PFC as well as in other regions of inhibitory networks still needs to be elucidated. As reviewed above, MPH has been shown to have effects on other networks, necessary to perform inhibitory tasks, such as the deactivation in the DMN, and the upregulation of performance and error monitoring networks. While ATX has also shown some effects on error monitoring networks in healthy adults, the effects of ATX on cognitive functions in patients with ADHD may differ from those on healthy subjects. Healthy adults with adequate NE levels would have these upregulated in excess by the administration of a single dose of ATX, which according to the reported inverted-U function of NE on cognitive performance may underlie the impaired performance in healthy adults (Graf et al., 2011). On the other hand, patients with

ADHD would show downregulated levels of NE, which would potentially be enhanced to an optimal level by the administration of a single dose challenge of ATX, improving their performance in the task.

There is only one study in time discrimination but the evidence of upregulating and normalising effects of MPH on key regions involved in these processes, including IFC, ACC and basal ganglia is consistent with the well-known role of DA in TD process.

Finally, during WM tasks, the little evidence for normalising effects on areas underactive compared to controls, suggests that MPH may work not by normalising regions typically involved in WM processes, but by upregulating prefrontal regions and basal ganglia, and by engaging and enhancing functional connectivity in widespread lateral prefrontal-cingulate-parietal networks. On the other hand, ATX compared to MPH in healthy adults has shown to downregulate more strongly the DMN during WM. However, whether these effects will be similar in ADHD patients still needs to be elucidated.

4.3. Limitations of the literature reviewed

Having reviewed the evidence, a number of factors need to be considered. Both neuropsychological and functional imaging studies suffer from the same caveats as those reviewed in Chapter 2. The inclusion of subjects with different subtypes of the disorder, comorbid conditions and different genders increase the heterogeneity of the samples and complicate the integration of the findings. As these factors were already extensively discussed in chapter 2 and therefore will not be further discussed in this section. However, the inclusion of subjects with a previous history of medication is of particular relevance for this section. The evidence on the long-term effects of persistent stimulant administration on brain structure and function (Frodin & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009) suggests that the recruitment of participants with a previous stimulant medication history introduces a major confounder. Thus, specially informative and valuable are those studies that have focused on medication naïve samples (Kratz et al., 2012; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009). Apart from these, all the other fMRI studies reviewed recruited subjects with a long-term history of stimulant medication, and tested them after a washout period either off their usual

medication or under a placebo condition. By including subjects that are under treatment and assessing them off and on their usual treatment we may be detecting a rebound effect on brain function. Using long enough washout periods is necessary to ensure both the lack of medication effects as well as the potential withdrawal effects of the drug. However, the potential effects of long-term adaptations on neural structure and function cannot be ruled out.

An important confound when interpreting the findings is the use of ROI methods. As described in Chapter 2, these methods are adequate when there is a strong *a priori* hypothesis, as it allows to restrict the number of comparisons conducted and therefore increases the power to detect differences (Poldrack, 2007). However, it leaves aside the potential involvement of other areas. This is particularly relevant for the reviewed studies, in particular with regards to the effects of MPH on brain function during motor response inhibition. Out of the studies conducted using motor response inhibition tasks, only one has used whole brain analysis (Rubia, Halari, Mohammad, et al., 2011). Thus, the available evidence may show some bias, with studies reporting consistently enhanced activation mainly in fronto-striatal regions by using ROI methods (Epstein et al., 2007; Vaidya et al., 1998). However, when whole brain methods are used, there are no upregulating effects of MPH within patients with ADHD, but the effects are stronger on IFC, basal ganglia, pre-SMA and temporo-parietal performance monitoring networks (Rubia, Halari, Mohammad, et al., 2011). As reviewed in a previous section of this chapter, MPH has been hypothesised to improve inhibitory performance not *per se* but by its effects on other processes such as motor execution (Bedard et al., 2003; Tannock et al., 1989; Tannock, Schachar, et al., 1995). Therefore, the study of the effects of MPH on brain activation seems to be at a stage where the use whole brain methods are needed to identify its true effects.

Ideally, a double blind design where neither the experimenter nor the subjects are aware of the condition they are being scanned under is desired. To do this, the use of a placebo condition is required. However, some studies have not used this placebo condition, but only tested their participants off-MPH, both in neuropsychological (Brackenridge et al., 2011; Langleben et al., 2006; Teicher et al., 2004) and fMRI studies (Kobel et al., 2009; Lee et al., 2010; Liddle et al., 2010; Peterson et al., 2009; Posner et al., 2011; Prehn-Kristensen et al., 2011; Vaidya et al., 1998). Although this is unavoidable in those cases where medication-naïve subjects are scanned at baseline and then again after long-term treatment, this is not appropriate for testing the effects

of a single dose of any of the drugs in patients that have been under treatment for some time. The lack of a placebo condition in these cases is a potential confound, as this makes it difficult to manage the potential expectations of the subjects about their performance in the tasks, and therefore on the brain activation observed. Placebo is a known medical phenomenon (Benedetti, 2005). Furthermore, the use of a placebo that appears identical to the medication helps to control the effects of expectation and masks the different conditions the patients are participating in, thus maintaining the blinding.

The presence of potential practice effects is another confound that the design of the studies typically have to try to minimise. In the case of within subjects studies, the randomisation of the conditions, the use of parallel versions of the tasks or a relatively long temporal lapse between sessions may have to dissipate or eliminate these potential effects. In the case of case-control studies, the testing of the healthy control group the same number of times so as to equalize the potential practise effects may be a solution. However, this is at a significant financial cost and ethical compromise. Nevertheless, if it can be shown that practice effects do not occur in the patient group, it can be assumed that they are unlikely to impact upon patient-control comparison.

CHAPTER 5. DESIGN AND AIMS OF THE PRESENT STUDY

5.1. Introduction

The evidence reviewed in chapters 1 and 2 demonstrates that ADHD is associated with neuropsychological deficits and reduced brain function during executive function processes, most consistently in tasks of motor response inhibition, working memory and additionally during temporal processes (Alderson et al., 2007; Cubillo et al., 2012; Lijffijt et al., 2005; Martinussen et al., 2005; Nigg et al., 2005; Rubia, 2011; Rubia, Smith, et al., 2007a; Rubia, Halari, Christakou, et al., 2009; Willcutt et al., 2005).

Despite the significant caveats of the studies reviewed in chapter 4, the findings suggest that MPH upregulates frontal, striatal, ACC and parietal regions during motor inhibition and TD tasks (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009; Vaidya et al., 1998), and enhances the deactivation of the DMN (including medial PFC and PCC regions) during different tasks (Liddle et al., 2010; Peterson et al., 2009). Furthermore, MPH has been shown to upregulate and normalise abnormally reduced activation in children with ADHD relative to controls in the IFC, ACC and basal ganglia during TD (Rubia, Halari, Christakou, et al., 2009). During WM tasks, however, the available evidence suggests that MPH may upregulate prefrontal regions and basal ganglia, and enhance functional connectivity in widespread fronto-cingulate-parietal cortical networks (Prehn-Kristensen et al., 2011; Wong & Stevens, 2012).

However, no fMRI study has as yet investigated the effects of ATX on brain function in ADHD patients, or compared the effects of ATX and MPH during any cognitive function in ADHD. The only available evidence is from studies in healthy adults, where ATX has been shown to enhance activation in key inhibitory regions, including the right IFC and STG (Chamberlain et al., 2009), in bilateral IFC during error processing (Graf et al., 2011) and to have deactivating effects on the DMN during WM (Marquand et al., 2011).

Taken together, neuropsychological and functional imaging studies show that MPH has important positive effects on cognition and brain activation in patients with ADHD. Furthermore, there is also emerging evidence from neuropsychological studies for the positive effects of ATX on performance in motor inhibition tasks in ADHD patients (Chamberlain et al., 2007; de Jong et al., 2009). However, more

studies have tested for potential positive effects of MPH on cognitive improvement than of ATX. Furthermore, the modulatory effects of ADHD medications on functional brain activation underlying cognitive performance has so far only been studied in patients with ADHD using MPH. Only a few fMRI studies have focused on the effects of MPH on brain activation in medication-naïve ADHD patients (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009). Most other studies were conducted in previously medicated patients. Consequently, the changes in brain activation may have been modulated by the previous stimulant medication and therefore any conclusions drawn from these studies can only be done so tentatively. Definite evidence on the compared effects of single dose challenges of MPH and ATX on brain networks can only be confidently concluded from studies on medication-naïve samples.

5.2. Design of the present study

This study investigates for the first time the compared effects of a single dose of MPH and ATX on brain activation in right-handed, non-comorbid, medication-naïve boys between 10 and 17 years of age with a clinical diagnosis of ADHD combined type during cognitive tasks where they typically present with cognitive deficits. These tasks are: a motor response inhibition task (SST), a parametric working memory task (N-Back) and a TD task.

For this purpose, participants were scanned three times in a double-blind, randomised, placebo-controlled, crossover design, which avoided the potential influence of the expectations of the subjects on the effects of the drugs. Furthermore, the randomised order of the drug administration was equally distributed to prevent the potential presence of practice effects between the three conditions. In order to maintain the double-blind design, all three medications were over-encapsulated using the same opaque capsules by the pharmacist. The psychiatrist collaborating in the study administered the medication on each occasion. This administration was based on pharmacokinetic evidence as reviewed in chapter 3, 1.5 hours before the scan to allow for maximum absorption (Chan et al., 1983; Witcher et al., 2003).

On each scanning session, they received a single dose of either placebo (Vitamin C, 50mg), MPH (Equasym, 0.3mg/kg, range 5–20mg) or ATX (Strattera, 1mg/kg, range 16–66mg), in a pseudo-randomized order, and remained medication-free

between scans. Dosages were determined following NICE guidelines of clinical efficacious dosages with minimal side effects at the time of the study (National Institute for Health and Clinical Excellence, 2008).

Brain activation under each drug condition was compared within patients to identify potential up- or down-regulation effects. To identify potential normalisation effects, an age-matched group of healthy control boys were recruited from the same South London geographical area, and they were scanned once, unmedicated. Brain activation in ADHD boys under each drug condition (placebo, MPH and ATX) was compared in each cognitive paradigm to that of the healthy control group, in order to identify abnormalities in brain function in ADHD boys when these were under placebo, and in order to test the potential normalisation effects of MPH and ATX on those brain dysfunctions.

Exclusion criteria for all participants were IQ<70 on the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999), history of substance abuse or neurological deficits, presence of psychiatric disorders (except for ADHD and CD/ODD in the ADHD group), learning disability, reading, speech or language disorder.

5.3. Sample selection and methods

The present study recruited only **medication-naïve children with ADHD**, in order to avoid the confound of the effects of a previous history of stimulant medication on brain activation. Chronic administration of stimulant medication is known to have long-term effects on brain structure and function (Frodl & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009), and is therefore a major confound in those studies aiming to identify the effects of MPH and/or ATX on cognition and brain function. The present study is therefore highly relevant and novel as the evidence from fMRI studies of the effects of ADHD medications on brain function during cognitive tasks in medication-naïve ADHD patients is scarce (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009) and non-existent in the case of ATX.

In this study, we recruited children with **pure ADHD**, without any comorbid disorders except for CD/ODD, which was present in 2 participants. The recruitment of patients with ADHD and comorbid disorders is an additional confound to previous

studies, even when the comorbid disorders are ODD/CD. These are highly comorbid with ADHD (30-50% of the cases) (Biederman et al., 1991; Spencer, 2006; Wilens et al., 2002), and it has been reported that children with pure ADHD compared to children with pure CD show shared and disorder specific abnormalities in brain activation (Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia, Smith, et al., 2009). This is important because the only way to rule out that the differences between groups with regards to cognitive deficits, brain activation or the effects of drugs are not due to the presence of comorbid conditions is by excluding them from the study. Therefore, any effects observed can be more confidently attributed to the presence of ADHD or the effects of drug administration and not to comorbid disorders.

In this study, **only boys** with ADHD were recruited, to increase the homogeneity of the sample and therefore the likelihood of detecting potential cognitive deficits, abnormal brain function and the effect of the two medications on these impairments. The inclusion of males and females in small samples reduces the homogeneity of the sample. Gender differences have been reported in ADHD patients in their cognitive profiles, brain function, presentation of the disorder and brain maturation (Balint et al., 2009; De Bellis et al., 2001; Gershon, 2002; Mahone & Wodka, 2008; Nigg et al., 2002; Rubia, Hyde, et al., 2010; Valera et al., 2010). In particular, the lack of brain dysfunction in females has been shown to overshadow brain deficits in males with ADHD (Valera et al., 2010). We therefore included only boys with the disorder, to increase the homogeneity of the sample.

The inclusion of different subtypes of the disorder is another factor that increases the heterogeneity of the samples. Although the combined subtype is the most commonly studied it is not infrequent to find that studies have collapsed the results of participants with different subtypes of the disorder. However, as discussed in chapter 1, there is still a debate about whether or not the combined and predominantly inattentive subtypes are etiologically similar or distinct entities (Barkley, 2001; Hinshaw, 2001; Milich et al., 2001; Swanson et al., 2007). Therefore, **only children with the combined subtype** of the disorder were recruited for the present study.

The selection of whole-brain or ROI methods is a highly relevant factor. The selection of ROI methods may be adequate in the presence of strong apriori hypotheses; however, it may bias the results towards certain areas and would miss

other regions where the two compounds may have an effect. This study used a combination of ROI and whole brain methods. Whole brain analyses were used for the case-control comparisons. The use of whole brain methods enabled the study to identify those regions where patients under placebo showed abnormal brain activation relative to controls, which may have not been hypothesised, but play a relevant role in the disorder, without the restrictions imposed by ROI methods to certain a-priori selected regions. We thought that this was important as previous fMRI studies in ADHD rarely exceed sample sizes of 20 participants. By recruiting 20 children with ADHD and 20 healthy controls, this study was relatively high powered and we did not want to miss important deficit regions. Furthermore, this also allowed for the study of the modulatory effects of both compounds on brain activation in these regions.

ROI analyses were conducted in the within patients contrasts. The main goal of this PhD was to study the compared effects of both drugs on those regions which are part of task-relevant neural networks and where children with ADHD typically present with reduced function. Thus, a mask was created for each task, taking as a reference those regions that where children with ADHD under placebo relative to controls showed reduced activation, as identified by whole brain analyses. This maximised the power of the study to detect the compared effects of each drug within patients in restricted task-relevant regions, which showed abnormal function in the ADHD group.

The use of a **single dose** of MPH and ATX avoids potential confounds associated to long-term treatment which may complicate the interpretation of the findings and the attribution of any changes in brain activation and performance to the drugs unequivocally. For example, the symptomatic improvement experienced by patients after prolonged administration of the drugs, the presence of side effects such as dizziness, nausea or sleepiness, and the potential chronic effects on brain structure and activation, which have so far only been described for MPH (Frodl & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009) are potential confounds associated with long-term treatment. Thus, the present study avoids such confounds by using a single dose of MPH and ATX.

5.4. Paradigms used

The selection of adequate paradigms also plays a highly relevant role. It is necessary to select tasks that have been shown to be sensitive both to the cognitive

deficits and underlying brain dysfunctions shown by children with ADHD, as also to the effects of single dose challenges of MPH and/or ATX. The evidence reviewed in chapters 1 and 2 allows to conclude that children with ADHD show deficits both in performance and brain activation in the underlying neural networks, most consistently during motor response inhibition processes as measured by the SST (Alderson et al., 2007; Lijffijt et al., 2005; Rubia, Halari, Mohammad, et al., 2011; Rubia, Smith, et al., 2007a; Rubia, Cubillo, et al., 2010; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005; Smith, Taylor, et al., 2006; Willcutt et al., 2005), during TD tasks (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008; Vloet et al., 2010) as well as in WM processes (Fassbender et al., 2011; Kobel et al., 2009; Sheridan et al., 2007; Silk et al., 2005; Vance et al., 2007). As reviewed in chapter 4, these deficits in performance and the underlying brain dysfunctions during these tasks have also shown to be sensitive to the administration of a single dose and prolonged MPH in ADHD patients, and also to the effects of ATX in the case of the SST in studies in healthy adults. Therefore, we selected a SST, and a TD task for use in this study.

MPH has been shown to have upregulation effects on prefrontal and striatal brain activation within children with ADHD during motor inhibition tasks (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998), while a single dose of ATX has shown upregulation effects in healthy adults in the key inhibitory area of right IFC during the SST (Chamberlain et al., 2009). There is also evidence for the key role of the left IFC during motor inhibition (Nee et al., 2007; Swick, Ashley, & Turken, 2008) and evidence that this region is upregulated with ATX in healthy adults during SST. Therefore, we expected that single doses of ATX and MPH would show comparable effects in inhibitory regions including bilateral IFC, with drug-specific effects for MPH on striatal activation, and perhaps slightly stronger effects for ATX given the evidence supporting the key role of noradrenaline during motor inhibition processes as measured by the SST (Bari et al., 2009; Eagle et al., 2008).

On the other hand, there is consistent evidence that dopamine is involved in time perception processes and neural networks (Rammsayer, 1999; Rubia, 2006) and there is evidence of upregulation and normalisation effects of MPH in key TD regions including IFC, ACC, striatum and cerebellum in medication-naïve children with ADHD (Rubia, Halari, Christakou, et al., 2009). Thus, we expected that a single dose of MPH but not of ATX would upregulate and normalise brain activation in TD neural networks.

Furthermore, as part of the Biomedical Research Centre program, the verbal N-Back Working Memory task is routinely administered. This is also a relevant task in the study of the effects of MPH and ATX in children with ADHD, given the relevance that verbal WM has in the academic achievement of these children (Gathercole & Alloway, 2006), which is frequently impaired. WM shown to be mediated by DA and NE in PFC (Gamo et al., 2010) and both MPH and ATX enhance NE and DA in PFC (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006). Furthermore, MPH in children with ADHD has shown upregulation effects in PFC and striatum during WM tasks (Prehn-Kristensen et al., 2011; Sheridan et al., 2010), while WM functions have shown to be sensitive to noradrenergic manipulations (Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006). Hence, we hypothesized that both drugs would modulate brain activation in PFC and that MPH would additionally do so in basal ganglia activation.

5.5 Conclusions

The comparison of the effects of single dose challenges of the two compounds on brain function in ADHD during cognitive processes that are problematic in ADHD would shed some light on the shared and drug-specific mechanisms of action of the two drugs in ADHD. It is currently not known whether MPH and ATX have drug-specific effects on cognitive functions that are typically impaired in ADHD or whether their modulatory effects on the underlying neural networks are similar or drug-specific. Although both drugs are routinely prescribed for the treatment of ADHD, it is not clear how they act on neural networks in ADHD patients. Given the lack of knowledge on the compared mechanisms of action of these drugs, at present, clinicians have to go through a trial-and-error process to identify the most appropriate medication and dose for each patient, with the accompanying delay in symptomatic improvement. Therefore, the study of the compared effects of a single dose challenge of MPH and ATX on brain activation would be a pioneering step towards the first knowledge of their drug-specific mechanisms of action, which would help to identify task-specific and shared effects of the two compounds on cognitive functions and the underlying neural networks. The use of a single dose instead of prolonged treatment avoids potential confounds of long-term treatment such as symptomatic improvement, and side effects of both drugs or their chronic effects on brain activation.

The differential effects of the two compounds on different cognitive functions and brain activation may eventually help to develop individually tailored treatment programs, based on the areas where a particular patient shows deficits and the specific action of the drugs.

The presence of drug-specific effects would furthermore help to understand the differential contribution of the catecholaminergic neurotransmitters DA and NE to the disorder. While both drugs share upregulation effects of DA and NE in PFC, only MPH has been shown to enhance DA availability in the basal ganglia. Whether the beneficial effects of ATX in ADHD are due to those shared prefrontal effects or whether it has differential effects on cognition and brain activation from those of MPH is not yet known. ATX is a selective pre-synaptic NET blocker (Bymaster et al., 2002), while MPH blocks both DAT and NET (Hannestad et al., 2010; Volkow, Wang, Fowler, Gatley, et al., 1998). Differential drug-specific modulatory effects of MPH and ATX on brain activation during a given cognitive task may suggest differential effects on catecholaminergic systems. This would indirectly shed light on the implication of DA and NE on the brain activation changes observed in ADHD after each medication, as well as indirectly increase our understanding on the neurotransmitters abnormalities present in ADHD patients compared to controls.

In conclusion, this study comparing the effects of MPH and ATX on brain activation of medication naïve children with ADHD during the performance of disorder-relevant tasks would lead to a first understanding of the compared mechanisms of action of the two compounds, and their differential effects may indirectly increase our knowledge of the underlying neurotransmitters involvement in ADHD during disorder-relevant tasks. Furthermore, a comparison of each drug's effect on brain function in ADHD relative to healthy controls would help to increase our understanding about their potentially shared and drugs-specific normalisation effects on brain function and cognition in the disorder.

CHAPTER 6: ATOMOXETINE AND METHYLPHENIDATE NORMALISE INHIBITORY DYSFUNCTION IN MEDICATION-NAIVE CHILDREN WITH ADHD

6.1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by age-inappropriate levels of impulsivity, inattention and hyperactivity (American Psychiatric Association, 2000). One of the most consistent findings are deficits in motor response inhibition, in particular during the SST (Alderson et al., 2007), underpinned by fMRI findings of reduced activation in key areas of motor response inhibition such as VLPFC, SMA and caudate (for reviews, see Cubillo et al., 2012; Rubia, 2011).

The stimulant MPH and the non-stimulant ATX are the most frequently prescribed drugs for the treatment of ADHD. However, their mechanisms of action in ADHD are relatively unknown. At therapeutic doses, MPH blocks 60-70% the dopamine transporter (DAT) in the striatum (Volkow, Wang, Fowler, Gatley, et al., 1998) and 70-80% of the norepinephrine transporter (NET) in NET-rich regions (Hannestad et al., 2010) including PFC, where it enhances extracellular levels of both NE and DA (Bymaster et al., 2002). ATX is a selective presynaptic NET blocker, which at therapeutic doses occupies NET almost completely in the ACC, thalamus, brain stem, midbrain, locus coeruleus and cerebellum (Gallezot et al., 2011).

Single dose MPH challenges in previously medicated children with ADHD have shown to upregulate frontal, striatal, ACC and parietal activation during GNG tasks (Epstein et al., 2007; Vaidya et al., 1998) and to normalise all brain activation deficits in VLPFC, SMA, parieto-temporal and cerebellar regions in medication-naïve children with ADHD during a SST (Rubia, Halari, Mohammad, et al., 2011). During other cognitive control functions, single dose MPH challenges in ADHD children have shown to upregulate or normalise most prominently fronto-striatal, but also temporo-parietal, cingulate and cerebellar activations (Rubia, Halari, Cubillo, et al., 2011; Shafritz et al., 2004).

In ADHD patients, no fMRI study has as yet investigated the effects of ATX or compared its effects with those of MPH during any cognitive function. In healthy adults, however, a single dose challenge of ATX upregulated VLPFC, STG and SMA activation during motor inhibition tasks (Chamberlain et al., 2009; Graf et al., 2011).

The aim of this study was to compare the effects of a single dose of MPH and ATX in medication-naïve ADHD boys during a challenging SST task using a randomised, double-blind, placebo-controlled, crossover design. To identify potential normalization effects, brain activation in the ADHD group under each drug condition was compared with that of a group of age-matched healthy boys. Based on previous studies on the SST, we hypothesized that medication-naïve ADHD boys under placebo compared to healthy boys would show reduced activation in VLPFC, SMA/ACC and caudate during successful inhibition (Pliszka, Glahn, et al., 2006; Rubia, Cubillo, et al., 2010; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005). We furthermore hypothesized that MPH would enhance frontal, striatal, SMA/ACC and parietal activation (Epstein et al., 2007; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998), while ATX would enhance activation of VLPFC and STG (Chamberlain et al., 2009; Graf et al., 2011).

6.2. Methods and materials

6.2.1. Participants

Sixty right-handed boys in the age range between 10-17 years participated in the study. Thirty medication-naïve right-handed boys were recruited from clinics. Patients had clinical diagnosis of ADHD, inattentive/hyperactive-impulsive combined subtype, as assessed by an experienced child psychiatrist using the standardized Maudsley diagnostic interview that assesses ADHD according to DSM-IV-TR criteria (Goldberg & Murray, 2002). A multidisciplinary clinical team participated in the assessment, which included information from semi-structured clinical assessment interviews with parents/carers, questionnaires from parents and teachers, school reports, developmental history, cognitive assessments and behavioural observation of the child. The presence of learning disability was concluded from the information provided by parents and school during the clinical and cognitive assessments, or by the presence of significant discrepancies between verbal and performance IQ subscores, which is considered as an indicator of potential learning difficulties.

ADHD boys scored above clinical threshold for hyperactive-impulsive/inattentive symptoms on the Strengths and Difficulties Questionnaire for parents (SDQ)(Goodman & Scott, 1999), the Conners' Parent Rating Scale (CPRS-R)(Conners et al., 1998), and below clinical threshold on the Social Communication

Questionnaire (SCQ)(Rutter et al., 2003)(Table 6.1). Patients were scanned in a double-blind, placebo-controlled, crossover design. On each scanning session, they received a single dose of either placebo (Vitamin C, 50mg), MPH (Equasym, 0.3mg/kg, range 5–20mg) or ATX (Strattera, 1mg/kg, range 16-66mg), in a pseudo-randomized order, and remained medication-free between scans. NICE guidelines of clinical efficacious dosages with minimal side effects at the time of the study were followed (National Institute for Health and Clinical Excellence, 2008). All three drug-conditions were over-encapsulated using the same capsules by the pharmacist. Based on pharmacokinetic evidence, both medications were administered 1.5 hours before the scan to allow for maximum absorption (Chan et al., 1983; Witcher et al., 2003). The same or similar dosages and time lapses between drug administration and scan have been shown to be sufficient to observe changes in brain activation and performance in ADHD patients (MPH)(Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011) and healthy controls (ATX)(Chamberlain et al., 2009).

Thirty healthy control boys were recruited through advertisement in the same geographical area and scanned once, unmedicated. They scored below clinical threshold on the SDQ, SCQ and CPRS-R (Table 6.1).

Exclusion criteria for all participants were IQ<70 on the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999), history of substance abuse or neurological deficits, presence of learning disability, reading, speech or language disorder, or other psychiatric disorder (except for CD/ODD in the ADHD group). When parental reports for potential participants were suggestive of the presence of such difficulties, questions addressing each of the criteria for ODD/CD were included in the semi-structured interviews. Thus, despite the fact that the mean score in the ADHD group for oppositional problems in the CPRS-R and behavioural difficulties in the SDQ scales were above clinical cut-offs (Table 6.1), only two cases received the formal diagnosis of ODD/CD.

Twelve participants (1 control, 11 ADHD boys) were excluded due to: above clinical threshold on the CPRS-R score in one control subject, IQ <70 (N=1), neurological abnormalities detected at the scan (N=1), technical problems that led to loss of data (N=3), incorrect performance of the task (N=1); inability to tolerate the scanning situation (N=4) or braces (N=1). Thus, the final sample consisted of 29

healthy control boys (mean age(SD)=13.9 (2.6)) and 19 medication-naïve children with ADHD (mean age(SD)=13.1m (1.7))(Table 6.1).

One-way analyses of variance (ANOVAs) showed no between-group differences for age ($F(1,46)=1.16;p=0.28$) but for IQ ($F(1,46)=28.07;p<0.001$)(Table 6.1). IQ scores have consistently been shown as lower in individuals with ADHD than in age-matched healthy controls (Bridgett & Walker, 2006; Kuntsi et al., 2004). Furthermore, IQ has shown to be moderately associated with inhibitory measures (Mahone et al., 2002). However, evidence from meta-analytic studies suggests this association may only partially underlie the deficits reported in children with ADHD during inhibitory functions. Thus, a recent meta-analytic study conducted meta-regression analyses and showed that IQ was not a moderator of the deficits observed in children with ADHD in the main performance variable of the SST, the SSRT, and was only a borderline moderator for the differences in mean reaction time of go responses (Lipszyc & Schachar, 2010). Similarly, another meta-analytic study reviewed the role of IQ in the differences reported by the different studies included in their meta-analyses, and concluded that differences in inhibitory measures may persist although weakened after controlling for IQ (Willcutt et al., 2005).

Hence, we conducted an exploratory analyses comparing brain activation between healthy controls and children with ADHD under placebo with and without using IQ as a covariate. When using IQ as a covariate, the resulting clusters of activation differences between groups included the same as when IQ was not used as a covariate, although at a higher p value ($p<0.03$), with the only exception of a small cerebellar/occipital cluster that was no longer observed. Hence, all the case-control comparisons for fMRI and performance data were conducted without using IQ as a covariate.

Table 6.1. Sample characteristics for healthy control boys and patients with ADHD.

Variables	Controls (29) Mean (SD)	ADHD (19) Mean (SD)
Age (years, months)	13y, 9m (2y, 6m)	13y, 1m (1y, 7m)
Age range (years, months)	10y, 3m – 17y, 10m	10y, 1m–15y, 6m
IQ	110 (12)	92 (11)
SDQ Total	4 (4)	22 (7)
SDQ Hyperactive-impulsive/ Inattentive Subscale	1(2)	8 (3)
SDQ Emotional difficulties subscale	1 (2)	4 (3)
SDQ Behavioural difficulties subscale	1 (1)	6 (3)
SDQ Getting along difficulties subscale	1 (1)	4 (3)
SDQ Kind and helpful behaviours subscale	9 (2)	5 (2)
SCQ Total	1 (1)	10 (5)
CPRS-R (DSM-IV) Total T score	44 (5)	79 (11)
CPRS-R oppositional T score	45 (4)	78 (11)
CPRS-R Cognitive/ inattention problems T Score	46 (4)	69 (9)
CPRS-R hyperactivity T score	47 (5)	81 (13)
CPRS-R anxious/shy T score	49 (8)	60 (16)
CPRS-R Perfectionism T score	44 (5)	59 (17)
CPRS-R social problems T score	46 (2)	60 (14)
CPRS-R Psychosomatic T score	48 (7)	63 (16)
CPRS-R Global Index: restless impulsive T score	45 (4)	78 (11)
CPRS-R Global Index: emotional liability T score	46 (6)	74 (13)
CPRS-R ADHD T score	46 (5)	76 (8)

Note: SDQ=Strengths and Difficulties Questionnaire; CPRS-R: Conners' Parent Rating Scale; SD= Standard Deviation

Participants received £50 per scanning session. Parental and child informed consent/assent and approval from the local Ethical Committee were obtained.

6.2.2. Experimental fMRI design: Stop task

Participants practiced once the 9-minutes mixed-trials, event-related fMRI Stop task, which measures the ability to suppress an already triggered motor response (Rubia et al., 2008; Rubia, Smith, et al., 2003; Rubia et al., 2005; Rubia, Smith, Taylor, et al., 2007). The basic go task is a choice reaction time task with a mean ITI of 1.8s, where subjects have to respond to go arrows (80% of trials, 236 trials) pointing either right or left with a right or left button response with the right/left thumb. In 20% of trials (60 trials), the go-signals are followed (about 250ms later) by stop-signals and subjects have to inhibit their motor responses (Figure 6.2). A tracking algorithm changes the time interval between go-signal and stop-signal onsets according to each subject's performance on previous trials based on the average percentage of inhibition over previous stop trials, recalculated after each stop trial, resulting in 50% successful and 50% unsuccessful inhibition trials.

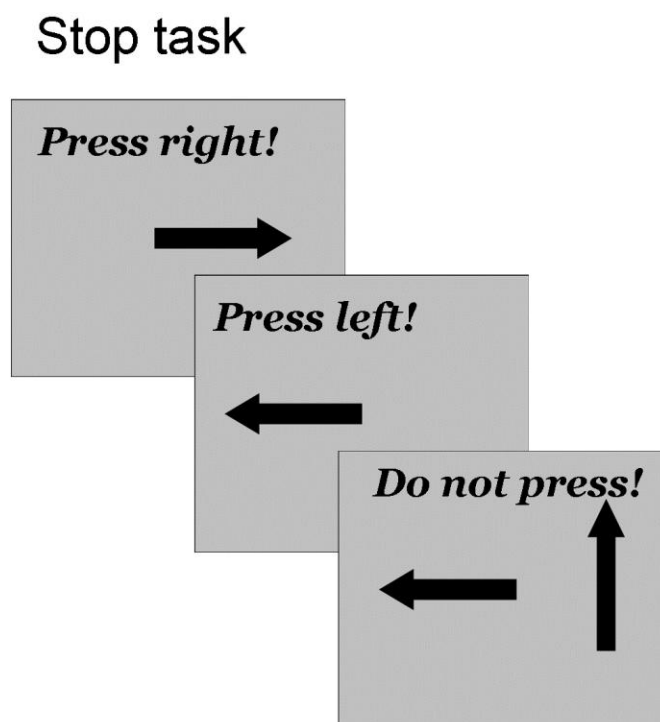


Figure 6.1. Stop task. Subjects have to respond to go arrows (79.6% of trials, 294 trials) that point either right or left with a right/left button response. In 20.4% of trials (60 trials), the go-signals were followed (about 250ms later) by stop signals and subjects had to inhibit their motor responses. A tracking algorithm changed the time interval between go-signals and stop-signals according to each subject's performance on previous trials (average percentage of inhibition over previous stop trials, recalculated after each stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials.

6.2.3. MRI image acquisition and analysis

Gradient-echo echoplanar MR imaging (EPI) data were acquired on a GE Signa 3T Horizon HDx system (General Electric, Milwaukee, WI, USA) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, UK. A semi-automated quality control procedure ensured consistent image quality (Simmons, Moore, & Williams, 1999). A quadrature birdcage headcoil was used for RF transmission and reception. In each of 28 non-contiguous planes parallel to the anterior-posterior commissure, 296 T₂*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with TE=30ms, TR=1.8s, flip angle=75°, in-plane resolution=3mm, slice thickness=5.5mm (including slice-skip=0.5mm). This EPI dataset provided almost complete brain coverage.

For fMRI analysis, the software package of XBAM was used (Brain Image Analysis Unit, 2011; Brammer et al., 1997) that makes no normality assumptions (violated in fMRI data), but instead uses median statistics to control outlier effects and permutation rather than normal theory-based inference. Furthermore, the most common test statistic is computed by standardising for individual differences in residual noise before embarking on second-level, multi-subject testing using robust permutation-based methods. This allows a mixed effects approach to analysis, recommended for fMRI (Thirion et al., 2007).

fMRI data were first processed to minimise motion related artifacts (Bullmore, Brammer, et al., 1999). A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x y and z axes) and translations (in x y and z) that maximised the correlation between the image intensities of the volume in question and the template (rigid body registration). Following realignment, data were

then smoothed using a Gaussian filter (FWHM, 7.2mm) to improve the signal to noise characteristics of the images.

After preprocessing, time series analysis for each subject was based on a wavelet-based data resampling method for functional MRI data (Bullmore et al., 2001; Bullmore, Brammer, et al., 1999). At the individual subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to the SST conditions (successful and failed stop trials) against an implicit baseline (go trials). Briefly, we first convolved the main experimental condition (successful and failed inhibitory trials, each separately contrasted with Go trials) with two Poisson model functions (peaking at 4s and 8s) after motion correction, global detrending and spin-excitation history correction. We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ-ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ-ratio for each subject, which were combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data.

After first-level analysis, the individual statistical maps were normalised into Talairach standard space (Bullmore et al., 2001). A group activation map was then produced for the experimental conditions by calculating the median SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). The voxel-level threshold was first set to $p < 0.05$ to give maximum sensitivity and to avoid type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters such that the final expected number of type I error clusters was < 1 per whole brain. Cluster mass rather than a cluster extent

threshold was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore, Suckling, et al., 1999).

ANOVAs were conducted using randomization-based tests for voxel or cluster-wise differences (Bullmore, Suckling, et al., 1999). Less than 1 false activated cluster was expected at a p-value of $p < 0.05$ for voxel and $p < 0.01$ for cluster comparisons. Thus, an expected cluster-level type I error rate of < 1 per brain was achieved by first applying a voxel-level threshold of $p < 0.05$ followed by thresholding the 3D clusters formed from the voxels that survived this initial step at a cluster-level threshold of $p < 0.01$. The cluster level threshold of $p < 0.01$, was therefore not applied to the whole brain (which would be lenient) but rather to the data previously thresholded at a voxel-wise level of $p < 0.05$. The necessary combination of voxel and cluster level thresholds is not assumed from theory but rather determined by direct permutation for each data set. In large connected clusters, we identified local maxima that were farther apart than the upper bound of the likely Talairach mapping error (3 voxel radius:10 mm) (Thirion et al., 2007). Voxels were then assigned to the nearest local maximum with a statistic value that exceeded that of the voxels. For each analysis, < 1 false positive 3D cluster per map were expected at a p-value of < 0.05 at the voxel-level and < 0.01 at the cluster-level.

For between-group comparisons, three ANOVAs were conducted comparing controls with patients under a) Placebo; b) MPH; and c) ATX. Within-subjects, we wanted to focus on the potential upregulation effects of either drug on brain regions that have shown to be typically impaired in ADHD patients during motor response inhibition tasks. Therefore, we chose as regions of interest, those areas that have been shown to be underactivated in ADHD patients in a recent meta-analysis of fMRI studies of Go/NoGo and Stop tasks (Hart, Radua, Nakao, et al., 2012). The areas that were found to be consistently underactivated in Go/NoGo and Stop tasks across 15 fMRI studies of motor response inhibition were the right VLPFC, SMA and ACC, left caudate and right thalamus (Hart, Radua, Nakao, et al., 2012). Based on these findings we therefore created an anatomical mask using the Talairach Client (Lancaster et al., 1997; Lancaster et al., 2000) which included the frontal lobes, the basal ganglia, the thalamus, and the ACC/SMA. Statistical measures of BOLD response were extracted in each of the clusters of within-group drug effects and post-hoc analyses were conducted to clarify the direction of these effects. Within patients, repeated measures

ANOVAs on the extracted BOLD response measures were conducted to test for potential order effects.

6.2.4. Performance data analysis

Multiple univariate ANOVAs were conducted between controls and patients under each drug condition (separately) in the main performance variables: the SSRT, calculated by subtracting the mean stop-signal delay (SSD: average time between go- and stop-signal, at which the subject inhibited 50% of stop trials) from the MRT to go trials, i.e. MRT-SSD (Rubia et al., 2008; Rubia, Smith, et al., 2003; Rubia et al., 2005; Rubia, Smith, Taylor, et al., 2007). Measures of the Go process of the task are the MRT to go trials and intra-subject standard deviation of MRT (SD of MRT). Repeated measures ANOVAs were conducted within patients to test for drug-condition effects (placebo, MPH, ATX) and for potential order effects.

6.3. Results

6.3.1. Task performance

There were no between-groups differences in the probability of inhibition ($F(3,82)=1.25$; $p<0.3$), demonstrating that the tracking algorithm was successful (Table 6.2). There were no significant performance differences between controls and patients under placebo. Patients under MPH showed a significantly shorter SSRT than controls ($F(1,46)=5.32$; $p<0.026$). Under ATX, patients relative to controls showed a reduced MRT to Go trials ($F(1,46)=5.04$; $p<0.03$) (Table 6.2).

Within-patients ANOVA showed a significant drug-condition effect on MRT to Go trials ($F(2,36)=3.28$; $p<0.049$), which was significantly reduced when patients were under ATX compared to placebo ($p<0.009$) (Table 6.2).

There were no order effects within patients.

Table 6.2. Performance data for 20 healthy control boys and 20 boys with ADHD under each medication condition

Performance Variable	Controls Mean (SD)	ADHD Placebo Mean (SD)	ADHD MPH Mean (SD)	ADHD ATX Mean (SD)
Pi (%)	51 (3)	51 (4)	53 (4)	53 (10)
MRT go trials (msec)	615 (117)	592 (77)	576 (79)	548 (71)
SD go trials (msec)	163 (56)	166 (50)	152 (42)	155 (65)
SSRT (msec)	165 (103)	126 (82)	93 (110)	133 (121)

Note: Pi = Probability of inhibition; MRT = Mean Reaction Time; SD = Intra-subject Standard Deviation; SSRT = Stop Signal Reaction Time; ATX = Atomoxetine; MPH = Methylphenidate

The performance of ADHD under placebo and healthy controls did not significantly differ in the main variable of the task, the SSRT. The group of patients showed a slightly shorter SSRT than healthy controls. However, this was only significantly shorter when patients were under MPH.

Given that the non-significant findings of the SSRT are not in line with the majority of neuropsychological studies (Alderson et al., 2007; de Zeeuw et al., 2008; Epstein, Langberg, et al., 2011; Lee et al., 2008; Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Martel et al., 2007; Nigg et al., 2005; Rommelse et al., 2008; Rubia, Smith, et al., 2007a; Willcutt et al., 2005), we further explored SSRT performance in ADHD patients. Table 6.3 shows the performance data of the group of ADHD boys depending on whether drug condition was administered during the first, second or third scanning session. In addition, Figure 6.2 shows the SSRTs for each group, as well as separately for each drug condition and scanning order.

Table 6.3. Detailed performance data of the 19 boys with ADHD in the main variables of the task under each drug condition and according to whether it was their first, second or third scanning session.

	FIRST SCAN	SECOND SCAN	THIRD SCAN
ADHD PLACEBO	SSRT: 177 (105)	SSRT: 93 (74)	SSRT: 122 (64)
ADHD MPH	SSRT: 60 (111)	SSRT: 109 (116)	SSRT: 116 (112)
ADHD ATX	SSRT: 139 (104)	SSRT: 160 (138)	SSRT: 99 (137)

Note: SSRT = Stop Signal Reaction Time; ATX = Atomoxetine; MPH = Methylphenidate

The small number of subjects in each group precludes from having enough power to confidently test whether there were order effects of the scanning session within each condition or, what could be even more important, the potential presence of sequence effects. SSRT of patients under placebo was numerically larger during the first scan, and numerically but not significantly shorter during the second and third scanning sessions, suggestive of potential albeit not statistically significant practice effects. However, this was not the case when ADHD boys were under MPH or ATX (see also Figure 6.2 below). Therefore, while practice effects may have been present under placebo, it seems unlikely that the significant differences in SSRT between healthy controls and patients under MPH are solely explained by such potential practice effects.

We furthermore explored the data to test whether the presence of potential outliers in any group or scanning session may have affected the group performance in any direction. However, as it can be seen in Figure 6.2 below, the only two subjects who were outliers were present in the control group. Results in task performance did not change after the exclusion of those two subjects.

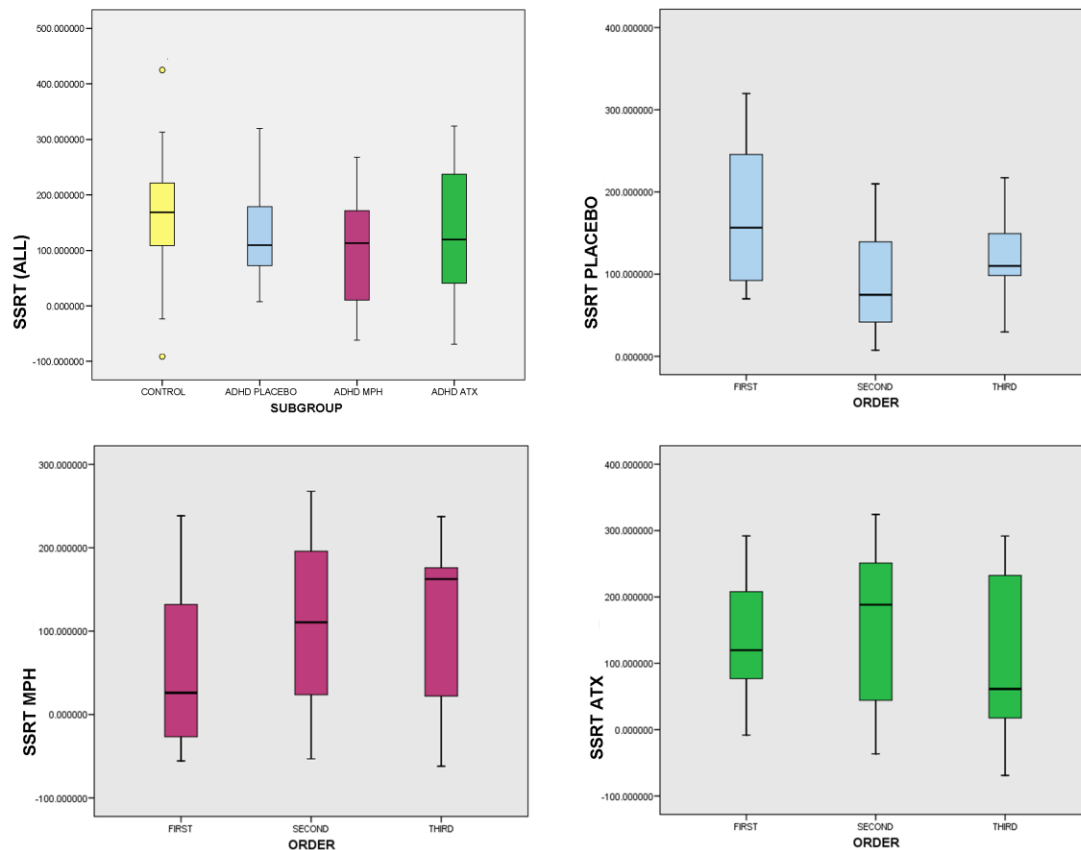


Figure 6.2. Mean and variability for each group in the main performance variable of the task (SSRT). On the top left, SSRT values and variability for each group (Controls, ADHD Placebo, ADHD MPH, ADHD ATX). On the top, right, SSRT values and variability within patients under placebo, depending on whether placebo was administered on the first, second or third scanning session. Down, on the left, SSRT values and variability within patients under MPH, depending on whether MPH was administered on the first, second or third scanning session. Finally, down on the right hand side, SSRT values and variability within patients under ATX, depending on whether ATX was administered on the first, second or third scanning session. MPH= Methylphenidate; ATX= Atomoxetine, SSRT= Stop Signal Reaction Time

6.3.2. Brain Activation

6.3.2.1. Motion

A multivariate ANOVA showed no significant differences between controls and patients under each drug-condition in the extent of maximum rotation and translation movement parameters in the 3-dimensional Euclidean space ($F(6,164)=1.56$, $p=0.16$).

6.3.2.2. Brain activation within groups

6.3.2.2.1. Successful inhibition – Go trials contrast

In the contrast of successful inhibitory trials compared to go trials, healthy boys showed activation in bilateral VLPFC and premotor regions, ACC extending to SMA, thalamus and subthalamic nuclei, inferior and superior temporal and parietal cortices, as well as in medial occipital regions and cerebellum. Furthermore, they showed activation in the right PCC, right putamen, left medial frontal gyrus, as well as in right medial and superior frontal areas (Table 6.4, Figure 6.3).

Children with ADHD under placebo showed activation in similar but less extensive bilateral VLPFC and premotor regions, insula, ACC and SMA, right putamen, STG, inferior and superior parietal regions, in occipital and parahippocampal cortices as well as in the cerebellum (Table 6.4, Figure 6.3).

ADHD boys under MPH showed enhanced activation during successful inhibitory trials in the bilateral VLPFC, premotor regions, ACC, putamen, thalamus, PCC, medial and superior temporal cortices, inferior and superior parietal lobes, occipital cortices (including parahippocampal gyrus) and cerebellum (Table 6.4, Figure 6.3).

When under ATX, boys with ADHD showed activation in right medial and superior frontal areas, bilateral VLPFC, premotor regions, ACC, SMA, putamen, thalamus and subthalamic nuclei, PCC, medial and superior temporal regions, inferior and superior parietal cortices, occipital gyri and cerebellum (Table 6.4, Figure 6.3).

6.3.2.2.2. Failed inhibition – Go trials contrast

During failed inhibitory trials compared to go trials, participants showed activation clusters that were very similar to those during the successful inhibition contrast, but less extended. This was the case in healthy controls, as seen in Figure 6.3 and Table 6.4.

Boys with ADHD under placebo also showed similar but less extended activation to that observed during successful inhibitory trials, although in this contrast the activation did not reach medial or superior prefrontal regions, and was particularly less extensive in VLPFC, PCC and parietal regions (Table 6.4, Figure 6.3).

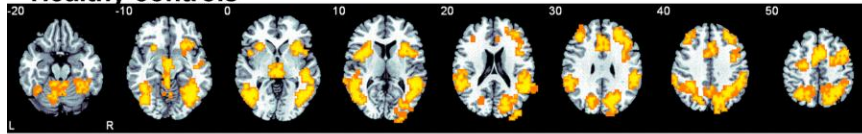
The activation observed in children with ADHD when under MPH was again very similar to that showed during the successful inhibition contrast, although in this case it was slightly more extensive in posterior temporo-parietal and thalamic regions, less extended in VLPFC and no longer comprised the ACC (Table 6.4, Figure 6.3).

Children with ADHD under ATX showed activation during inhibition failures in the same regions as during successful inhibition trials, although in this case it did no longer reach the left VLPFC, and was much less extended in the right VLPFC, medial and superior prefrontal regions (Table 6.4, Figure 6.3).

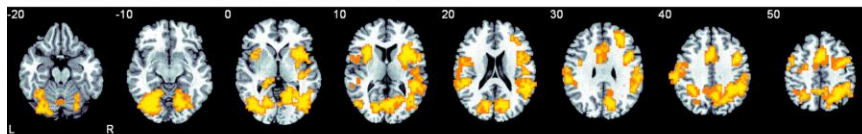
Within-group activations

a) Successful inhibition – Go trials contrast

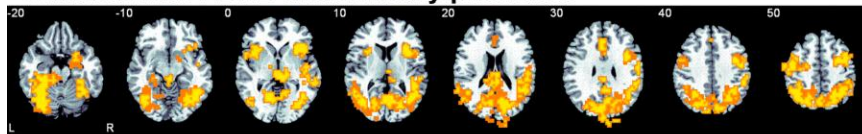
Healthy controls



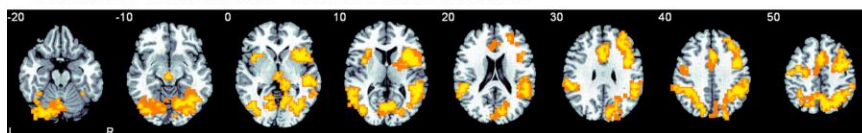
Children with ADHD under Placebo



Children with ADHD under Methylphenidate

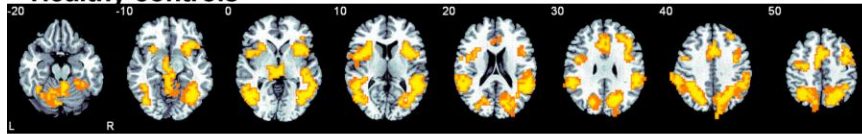


Children with ADHD under Atomoxetine

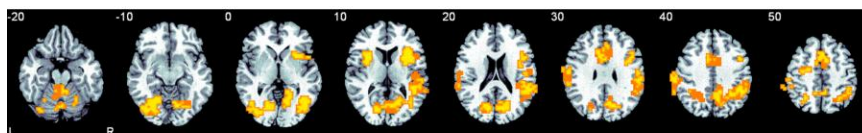


b) Failed inhibition – Go trials contrast

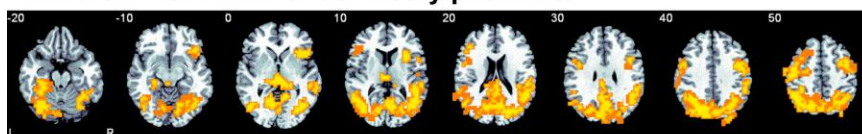
Healthy controls



Children with ADHD under Placebo



Children with ADHD under Methylphenidate



Children with ADHD under Atomoxetine

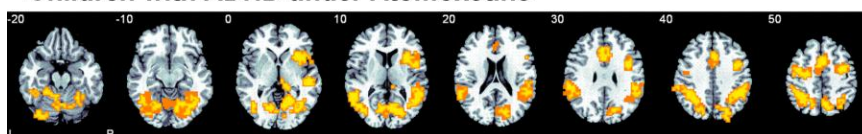


Fig 6.3. Within-group activation for healthy control boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine. Axial sections showing within-group brain activation for the healthy comparison boys and boys with ADHD under each condition (placebo, MPH, ATX) for the contrasts a) Successful Inhibition – Go trials, b) Failed inhibition – Go trials. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 6.4. Brain Activation within each group for the contrasts a) Successful inhibition- Go trials and b) Failed inhibition – Go trials

Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	P value
a) Successful inhibition- Go trials contrast				
Healthy control boys				
R inferior/medial/superior frontal/premotor gyri/insula/putamen	44/45/47/9/10/46/4/6	29; 22; 0	495	<0.001
L inferior frontal/premotor/insula/putamen	44/45/47/6	-25; 19; 10	159	<0.001
L medial frontal gyrus	9/46	-36; 37; 26	57	0.003
R + L anterior cingulate/mesial prefrontal cortex/supplementary motor area/premotor gyri	24/32/8/6	4; 11; 43	414	<0.001
R subthalamic nuclei/globus pallidus/R+L thalamus	-	4; -15; -3	273	<0.001
R posterior cingulate/ postcentral/ medial/superior temporal/inferior/superior parietal/ cuneus/precuneus/occipital gyri/cerebellum	31/1/2/3/21/37/22/42/40/7/18/19	54; -41; 13	1340	<0.001
L inferior/superior parietal gyri/cuneus/precuneus	40/7/19	-25; -52; 40	248	<0.001
R medial occipital gyrus	19	43; -85; 13	43	0.003
L inferior/medial/superior temporal/inferior parietal/occipital gyri/cerebellum	21/37/39/22/40/19	-43; -59; -3	444	<0.001
Boys with ADHD under PLACEBO				
R inferior frontal/premotor/insula/putamen/superior temporal gyri	44/45/47/4/6/22	29; 22; 7	427	<0.001
L inferior frontal/premotor gyri/insula/putamen/medial frontal gyri	44/45/4/6	-29; 26; 7	110	<0.001
R medial/superior frontal gyri	10/46/9	29; 37; 26	56	0.001
R + L anterior cingulate/mesial prefrontal/supplementary motor area	24/32/8/6	4; 11; 43	248	<0.001
L premotor/postcentral/superior temporal/inferior parietal gyri	4/6/1/2/3/22/40	-47; -33; 13	169	<0.001

L inferior/superior parietal gyri	40/7	-29; -56; 56	120	<0.001
R posterior cingulate/postcentral/inferior/medial/superior temporal/inferior/superior parietal/cuneus/precuneus/occipital/parahippocampal gyri/cerebellum	23/30/31/1/2/3/43/37/39/2 1/22/42/17/18/19/40/7	47; -37; 13	1331	<0.001
L hippocampus/parahippocampal/inferior/medial temporal/occipital gyri/cerebellum	37/21/18/19	-43; -63; 0	442	<0.001
R + L cerebellum	-	-32; -48; -46	208	<0.001
Boys with ADHD under MPH				
R inferior frontal/premotor gyri/insula/putamen/hippocampus/amygdala	45/47/6	29; 22; 3	194	<0.001
R inferior frontal/premotor gyri	44/4/6	36; 0; 33	154	<0.001
L inferior frontal gyrus/insula	45/47	-25; 22; 3	85	0.001
R + L anterior cingulate	24/32	0; 33; 23	49	0.003
L pre/postcentral gyri	4/6/1/3	-25; -4; 53	118	<0.001
L medial/superior temporal/inferior parietal gyri	39/22/40	-36; -67; 10	172	<0.001
L hippocampus/parahippocampal/inferior temporal/occipital gyri/cerebellum	37/18/19	-29; -59; -23	508	<0.001
R inferior/medial/superior temporal/postcentral/occipital gyri/cerebellum/ R + L thalamus/posterior cingulate/inferior/superior parietal gyri/cuneus/precuneus	37/39/21/22/42/43/18/19/2 3/30/31/40/7	4; -30; 20	2213	<0.001
Boys with ADHD under ATX				
R inferior/medial/superior frontal/premotor gyri/insula/putamen	44/45/47/8/9/10/46/6	36; 22; 0	560	<0.001
L inferior frontal gyrus/insula/putamen	45	-29; 22; 10	50	0.002
R + L anterior cingulate/mesial frontal gyri/supplementary motor area	24/32/6/8	4; 11; 43	278	<0.001
R + L thalamus/subthalamic nuclei	-	4; -19; -10	82	0.003
L premotor (precentral gyrus)	4/6	-25; -7; 52	70	0.002
R + L posterior cingulate/postcentral/inferior/medial/superior temporal/inferior/superior parietal/cuneus/precuneus/occipital gyri/cerebellum	23/31/1/2/3/37/21/22/40/7/ 18/19	54; -37; 7	1808	<0.001
b) Failed inhibition – Go trials contrast				

Healthy control boys				
R inferior/medial/superior frontal/premotor gyri/insula/putamen	44/45/47/9/46/6	32; 22; -3	251	<0.001
L inferior frontal/premotor gyri/insula/putamen	44/45/47/4/6	-32; 15; 7	268	<0.001
R + L anterior cingulate/mesial prefrontal cortex/supplementary motor area/premotor gyri	24/32/6/8	31; 22; 36	575	<0.001
R thalamus/subthalamic nuclei	-	4; -19; -3	147	<0.001
R posterior cingulate/ postcentral/ medial/superior temporal/inferior/superior parietal/ cuneus/precuneus/occipital gyri/cerebellum	31/1/2/3/21/37/22/42/40/7/18/19	51; -37; 13	1112	<0.001
L inferior/medial/superior temporal/inferior/superior parietal/cuneus/precuneus/occipital gyri/cerebellum	21/37/39/22/40/7/18/19	-43; -59; -3	757	<0.001
L cerebellum	-	-11; -70; -30	96	0.002
R cerebellum	-	4; -52; -20	75	0.002
Boys with ADHD under PLACEBO				
R inferior frontal/premotor/insula/putamen/superior temporal gyri	44/45/47/4/6/22	36; 15; 7	191	<0.001
L inferior frontal gyrus/insula	45	-29; 19; 7	40	0.002
R + L anterior cingulate/supplementary motor area	24/32/6	0; 11; 43	128	<0.001
R precentral gyrus	4/6	-14; -4; 63	56	0.002
L postcentral gyrus	1/2/3/43	-58; -11; 23	102	<0.001
L inferior/superior parietal gyri	40/7	-29; -56; 56	58	0.002
R posterior cingulate/postcentral/inferior/medial/superior temporal/inferior/superior parietal/cuneus/precuneus/occipital/parahippocampal gyri/cerebellum	23/31/1/2/3/43/37/39/21/22/42/17/18/19/40/7	47; -37; 13	992	<0.001
L inferior/medial temporal/occipital gyri/cerebellum	37/21/18/19	43; -63; -3	83	<0.001
R + L cerebellum	-	0; -59; -30	133	<0.001
Boys with ADHD under MPH				
R inferior frontal/premotor gyri/insula/putamen	45/47	36; 26; 0	104	<0.001
R inferior frontal/premotor gyri	44/4/6	40; 7; 46	123	<0.001

L inferior frontal gyrus	45	-43; 33; 13	27	0.004
L pre/postcentral/superior frontal gyri	4/6/1/3/8	-51; -4; 43	177	<0.001
R+ L thalamus/posterior cingulate/inferior/medial/superior temporal/postcentral/inferior/superior parietal/cuneus/precuneus/occipital gyri/cerebellum	23/30/31/37/39/21/22/42/ 43/40/718/19	-18; -67; 40	2847	<0.001
Boys with ADHD under ATX				
R inferior/premotor gyri/insula/putamen	44/45/47/4/6	36; 15; 7	170	<0.001
R inferior frontal/premotor gyri	44/4/6	36; 0; 49	94	<0.001
R + L anterior cingulate/mesial frontal gyri/supplementary motor area	24/32/6/8	4; 11; 49	237	<0.001
L premotor (precentral gyrus)	4/6	-25; -7; 49	75	0.002
R thalamus	-	18; -33; -7	67	0.004
R precuneus	7	11; -63; 46	61	0.004
R + L posterior cingulate/postcentral/inferior/medial/superior temporal/inferior/superior parietal/cuneus/precuneus/occipital gyri/cerebellum	23/31/1/2/3/37/21/22/40/7/ 18/19	18; -56; 0	1506	<0.001

Note: N voxels = number of voxels. L = left; R = right. The maps are thresholded to give less than 1 Type I3D error cluster per map

6.3.3. ANOVA comparisons between controls and ADHD boys under each drug condition

6.3.3.1. Successful inhibition – Go trials contrast

Controls compared to ADHD patients under placebo

Compared to healthy controls, ADHD boys showed underactivation in left and right VLPFC, left MTG and inferior temporal gyrus (ITG) reaching into IPL and right anterior cerebellum/fusiform gyrus (Table 6.5, Figure 6.4).

Patients showed enhanced activation compared to controls in a cluster comprising left posterior cerebellum/PCC, and in right STG, reaching into posterior insula and putamen (Table 6.5, Figure 6.4). Given prior evidence for enhanced posterior cerebellum/PCC activation in ADHD to compensate for reduced VLPFC activation (Cubillo et al., 2012; Rubia, Smith, et al., 2009) we used one-tailed Pearson correlations within patients on the BOLD response in these two enhanced activation clusters to test whether they were negatively correlated with the reduced VLPFC clusters. Only activation in the right STG-putamen, but not the cerebellum, was negatively correlated with that of left VLPFC ($r = -0.39$, $p < 0.05$).

To test whether areas of group differences were associated with inhibitory function, one-tailed Pearson correlations were performed between BOLD responses in these regions and SSRTs within each group. Within healthy boys, the (enhanced) activation in right cerebellum was correlated with shorter SSRT ($r = -0.45$, $p < 0.007$). Within patients, the (enhanced) activation in the right STG-putamen was negatively correlated with SSRT ($r = -0.41$, $p < 0.04$).

Post-hoc analyses were conducted to examine the linear relationship between IQ and brain activation differences. There were no significant correlations between BOLD signal in any of the clusters of activation differences and IQ within patients ($p > 0.4$) or controls ($p > 0.5$).

Controls compared to ADHD patients under MPH

ADHD boys under MPH compared to controls showed reduced activation in the same left MTG cluster (Table 6.5, Figure 6.4). All other previously reduced activation clusters were no longer observed.

Patients under MPH showed enhanced activation compared to healthy boys in three clusters, 1) bilateral occipital cortex, PCC and precuneus, 2) left occipital cortex and cerebellum, and 3) left occipital and MTG/IPL (Table 6.5, Figure 6.4).

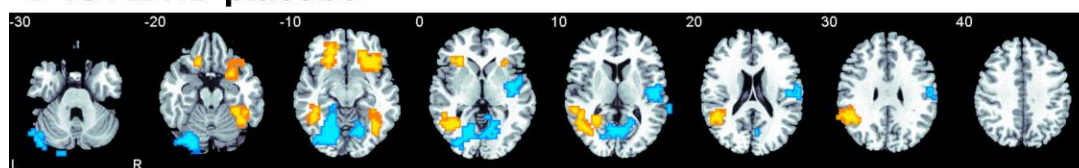
Within patients, the enhanced activation in left cerebellum was negatively correlated with SSRT ($r=-0.44$, $p<0.03$). Within controls, there were no significant associations between brain activation and SSRT.

Controls compared to ADHD patients under ATX

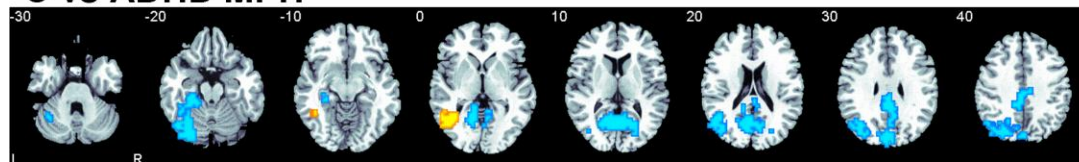
After ATX, patients relative to controls showed reduced activation in the same left MTG cluster and, as with MPH, all other previously reduced activation clusters were no longer observed (Table 6.5, Figure 6.4). There were no areas of enhanced activation in patients and no significant associations between brain activation and SSRT within patients or controls.

Successful inhibition – Go trials

C vs ADHD placebo



C vs ADHD MPH



C vs ADHD ATX

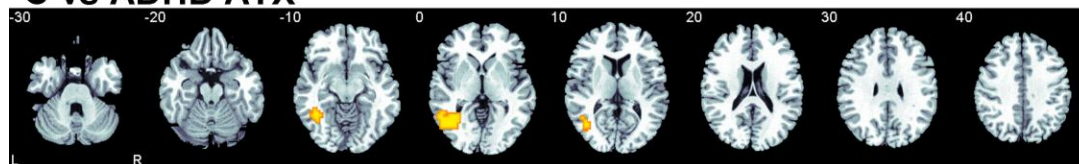


Figure 6.4. Between-group ANOVA comparisons between healthy control boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine for the successful inhibition-Go trials contrast. Axial sections showing the ANOVA between-group differences in brain activation between healthy control boys and boys with ADHD under each drug condition (Placebo, MPH, ATX) during successful inhibition in the Stop task. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

In order to test for potential effects of IQ on group differences in brain activation, the analyses were repeated with IQ as a covariate. All findings remained significant at a more lenient p value ($p < 0.03$) (See Appendix Figure A1).

Table 6.5. ANOVAs comparing controls and ADHD patients under each drug during successful motor response inhibition in the Stop task

Subject Contrast	Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	Cluster P value	Cohen's <i>d</i>
C > ADHD Plac	R inferior frontal gyrus	47/11	32; 30; -10	156	0.009	0.67
	L inferior frontal gyrus	45/47	-22; 33; -13	110	0.01	1.16
	L middle/inferior/temporal/parietal gyri	21/37/22/40	-43; -52; 0	287	0.002	1.22
	R cerebellum/fusiform gyrus	36/37	36; -59; -10	97	0.01	1.06
ADHD Plac > C	L cerebellum/R + L posterior cingulate/occipital gyri	29/30/31/18/19	-25; -70; -16	637	<0.001	1.00
	R superior temporal/postcentral gyri/posterior insula/putamen	42/22/21/4	47; -15; 7	190	0.008	1.03
C > ADHD MPH	L middle temporal gyri	21/37	-40; -59; -3	108	0.005	0.91
ADHD MPH > C	L cerebellum/parahippocampus/occipital gyri	36/37	-29; -37; -26	201	0.005	1.18
	L occipital/middle temporal/precuneus	39/22/40/7/19	-32; -70; 27	243	0.003	0.50
	L + R occipital gyri/posterior cingulate/precuneus	23/29/30/31/7/18/19	-11; -52; -3	624	<0.001	1.19
C > ADHD ATX	L middle temporal gyrus	21/37	-40; -56; -7	156	0.003	1.23
ADHD ATX > C	Nil					

Note: N voxels = number of voxels. L = left; R = right; the maps are thresholded to give less than 1 Type I error 3D cluster per map. Talairach coordinates, number of voxels and areas are included underneath the corresponding cluster.

6.3.3.2. Failed inhibition – Go trials contrast

Controls compared to ADHD patients under placebo

Children with ADHD under placebo compared to healthy boys showed underactivation in the same regions as in the successful inhibition contrast, with some exception: there was no underactivation in left VLPFC, the reduced activation in temporal region was bilateral and reaching more dorsally parietal regions, and there was an additional cluster of reduced activation in children with ADHD relative to controls comprising the thalamus (Table 6.6, Figure 6.5).

There were no significant correlations between BOLD signal in any of the clusters of between-group activation differences and IQ within patients ($p>0.1$) and controls ($p>0.5$).

Controls compared to ADHD patients under MPH

The pattern of activation differences was almost identical to that observed in the successful inhibition contrast, with the exception of the cluster of reduced activation in left MTG in patients with ADHD under placebo, which was no longer observed in the failed inhibition contrast (Table 6.6, Figure 6.5).

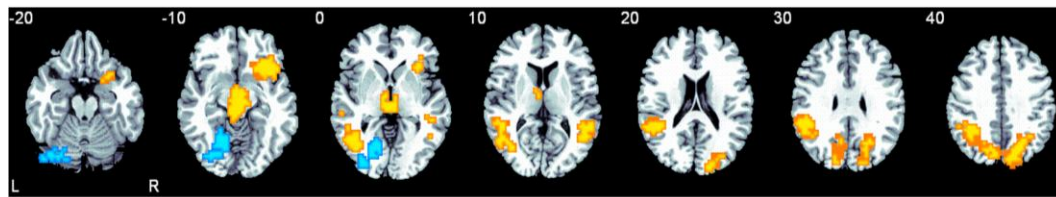
Controls compared to patients under ATX

As in the successful inhibition contrast, children with ADHD under ATX relative to healthy boys only showed reduced activation in the same clusters when under placebo of reduced activation located in temporal regions, which in this contrast were bilateral (Table 6.6, Figure 6.5).

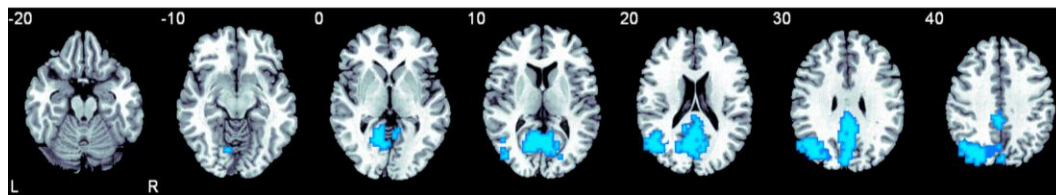
When IQ was used as a covariate, most findings remained significant at a more lenient p value ($p<0.03$) with the exception of the clusters in the thalamus and left temporal cortex that were no longer observed.

Failed inhibition – Go trials

C vs ADHD placebo



C vs ADHD MPH



C vs ADHD ATX

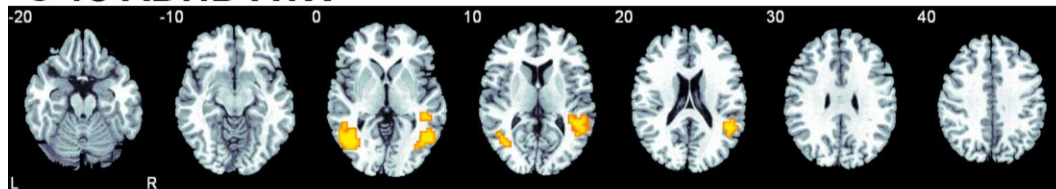


Figure 6.5. Between-group ANOVA comparisons between healthy control boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine for the contrast failed inhibitory – go trials. Axial sections showing the ANOVA between-group difference effects in brain activation between healthy control boys and boys with ADHD under each condition (placebo, MPH, ATX) during the Failed inhibition condition of the task. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 6.6. ANOVAs comparing controls and ADHD patients under each drug during failed motor response inhibition in the Stop task

Subject Contrast	Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	Cluster P value	Cohen's <i>d</i>
<i>Failed Stop – go trials</i>						
C > ADHD Plac	R inferior frontal gyrus/insula	45/47	36; 26; -13	133	0.008	0.87
	R+L thalamus/subthalamic nuclei/tail of caudate	-	0; -19; -7	165	0.01	0.82
	R middle temporal gyri	21/22	47; -44; 3	87	0.01	1.02
	L middle temporal/inferior/superior parietal gyri	21/22/40/7	-36; -56; -3	441	0.001	1.34
	R cuneus/precuneus	7/18	25; -56; 27	167	0.01	1.22
ADHD Plac > C	L occipital/parahippocampal gyri/cerebellum	18/19	-18; -63; -7	284	0.005	1.02
C > MPH	Nil					
ADHD MPH > C	R + L posterior cingulate gyrus/precuneus	31/7	0; -74; 23	595	<0.001	0.77
	L occipital gyrus	19/19/39	-22; -70; 36	314	0.001	1.14
C > ADHD ATX	L medial temporal gyrus	21/22	-43; -59; -3	91	0.007	1.13
	R medial temporal gyrus	21/22	47; -44; 3	153	0.004	0.43
ADHD ATX > C	Nil					

Note: N voxels = number of voxels. L = left; R = right; the maps are thresholded to give less than 1 Type I error 3D cluster per map. Talairach coordinates, number of voxels and areas are included underneath the corresponding cluster.

6.3.4. Significance of the “normalization” effects

We wanted to analyze the significance of the “normalization” effects observed in the between-groups fMRI analysis. Given that the data of the healthy control group was identical across the different case-control comparisons, non-parametric Friedman tests were conducted only within patients to identify whether there were significant differences in brain activation under each drug condition in each of those clusters where the case-control contrasts showed “normalization” effects.

For the successful inhibition contrast, there were significant differences between drug conditions in the right VLPFC (BOLD Placebo: -0.007; BOLD MPH: 0.013; BOLD ATX: <0.001; χ^2 (2, N=19) = 8.84, $p < 0.012$), which, as shown by post-hoc non-parametric Wilcoxon Tests, was due to significant enhanced activation when under MPH relative to placebo ($p < 0.04$) and also to ATX ($p < 0.05$). In the cluster of left VLPFC, there was a trend for activation differences between the three drug conditions (BOLD Placebo: -0.022; BOLD MPH: <0.001; BOLD ATX: -0.005; χ^2 (2, N=19) = 5.16, $p < 0.076$), due to the significant differences between Placebo and MPH ($p < 0.016$), as well as between Placebo and ATX ($p < 0.030$). In the occipito-cerebellar cluster, however, there were no significant differences between conditions (BOLD Placebo: <-0.001; BOLD MPH: 0.024; BOLD ATX: 0.017; χ^2 (2, N=19) = 1.26, $p < 0.53$), although post-hoc analyses showed significant differences between placebo and MPH drug conditions ($p < 0.04$) and at a trend level, between placebo and ATX ($p < 0.1$).

In the failed inhibition contrast, there was a trend for significant differences in brain activation between the three drug conditions in the right VLPFC (BOLD Placebo: -0.007; BOLD MPH: 0.011; BOLD ATX: 0.003; χ^2 (2, N=19) = 5.47, $p < 0.06$), which was due to the differences between placebo and MPH ($p < 0.022$) and, at a trend level, with ATX ($p < 0.084$), suggesting that only MPH had a significant “normalisation” effect on this region relative to placebo. Similarly, there was a trend for significant differences on brain activation in the thalamus (BOLD Placebo: -0.003; BOLD MPH: 0.007; BOLD ATX: 0.008; χ^2 (2, N=19) = 5.03, $p < 0.08$), due to almost significant differences between activation under placebo relative to MPH ($p < 0.077$) and ATX ($p < 0.077$), which did not differ between them. In the right temporal cortex, there were no significant differences between brain activation under the three drug conditions (BOLD Placebo: 0.013; BOLD MPH: 0.028; BOLD ATX: 0.037; χ^2 (2,

N=19) = 1.37, $p < 0.50$), however, there were significant differences in the right parietal region (BOLD Placebo: -0.001; BOLD MPH: 0.022; BOLD ATX: 0.015; χ^2 (2, N=19) = 8.84, $p < 0.012$), due to the differences between brain activation observed when patients were under Placebo relative to MPH ($p < 0.007$) and ATX ($p < 0.022$). Finally in the cluster of activation in the left temporal cortex, significant differences between the three drug conditions were observed (BOLD Placebo: -0.003; BOLD MPH: 0.018; BOLD ATX: 0.013; χ^2 (2, N=19) = 11.47, $p < 0.003$), due to the differences between the Placebo and MPH conditions ($p < 0.005$) as well as between Placebo and ATX ($p < 0.004$).

6.3.5. ANOVA within-patients comparison between placebo, MPH and ATX conditions

Within-group effects of each drug condition were tested in the anatomically defined ROIs of frontal lobe, SMA/ACC, basal ganglia and thalamus in the two contrasts of successful and failed inhibition versus go trials. As described in the methods section, the selection of such ROIs was based on the results from a previous meta-analysis of 15 fMRI studies of motor response inhibition showing that ADHD children have consistent underactivation in these regions relative to controls, i.e. in right VLPFC, SMA and ACC, left caudate and right thalamus (Hart, Radua, Nakao, et al., 2012).

6.3.5.1. Successful inhibition – Go trials contrast

For the successful inhibition contrast, there was a main effect of drug condition within patients in a cluster in the SMA that reached ventrally into the ACC (103 voxels, peak Talairach coordinates (x;y;z): 7; 11; 43; BA 6/32; $p < 0.001$). This was due to the significantly enhanced activation during Go responses in patients under MPH compared to ATX ($p < 0.001$) and placebo ($p < 0.001$), the latter of which did not differ from each other ($p < 0.79$) (Figure 6.6). There were no other significant drug effects on any other ROI.

There were no significant order effects on brain activation.

6.3.5.2. Failed inhibition – Go trials contrast

In the failed inhibition contrast, there was a main effect of condition in 2 clusters (Figure 6.7). One cluster comprised the left MFC, extending to SFC (51 voxels, peak Talairach coordinates (x;y;z):-25;41;16; BA 9/10/46; $p<0.008$), due to enhanced activation during Go trials in patients under MPH relative to when under placebo ($p<0.003$) and ATX ($p<0.033$), with a trend for enhanced activation during Go trials when under ATX relative to placebo ($p<0.09$). A second cluster of activation differences was observed in the same SMA/ACC region that emerged during the successful inhibition contrast (80 voxels, peak Talairach coordinates (x;y;z):7; 11; 43; BA 6/32; $p<0.001$). Brain activation differences in this region were due to significantly enhanced activation during Go trials in patients when under MPH relative to ATX ($p<0.001$) and Placebo ($p<0.001$), which did not differ between them ($p<0.3$). No other drug effects were observed in any of the ROIs.

There were no significant effects of order on brain activation.

REPEATED MEASURES ANOVA ANALYSES ON DRUG EFFECTS WITHIN ADHD BOYS DURING SUCCESSFUL INHIBITION

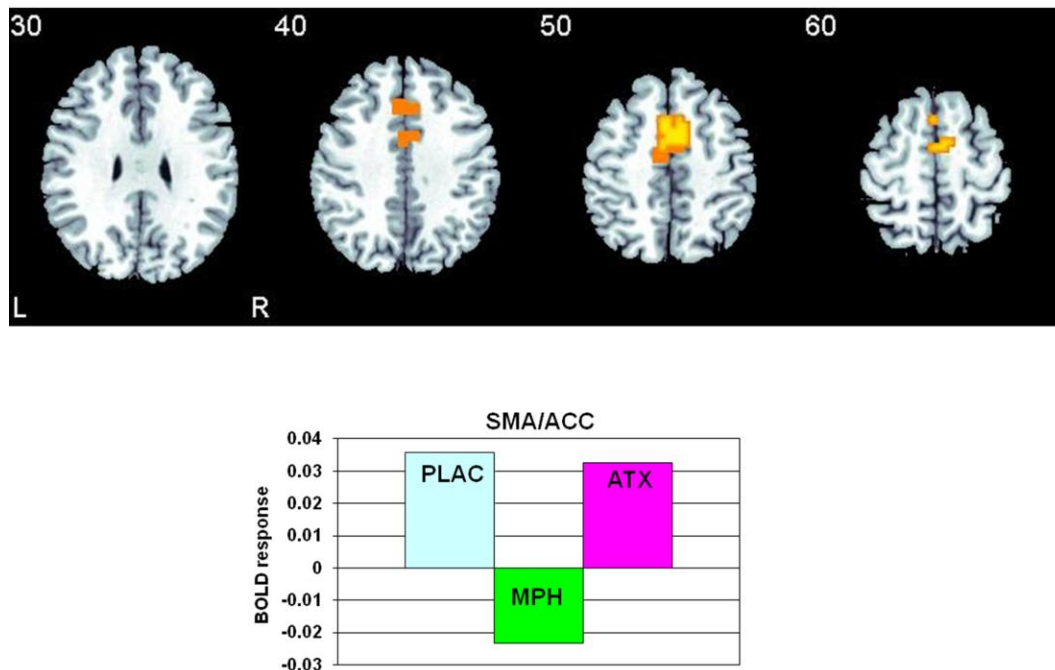


Figure 6.6. Results of the repeated measures ANOVA analysis on drug effect within ADHD boys during the Successful inhibition – Go trials contrast. Axial sections showing the repeated measures ANOVA results for the drug effect within ADHD patients (Placebo, MPH, ATX). Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

REPEATED MEASURES ANOVA ANALYSES ON DRUG EFFECTS WITHIN ADHD BOYS DURING FAILED INHIBITION

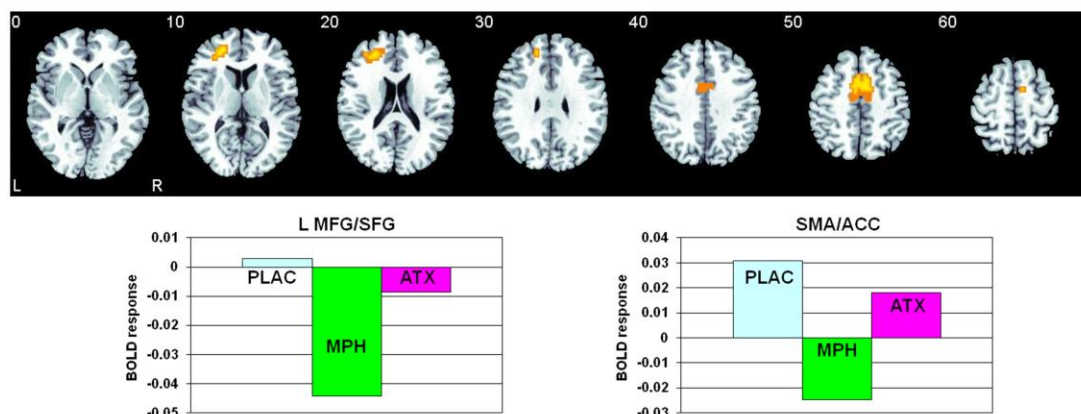


Figure 6.7. Results of the repeated measures ANOVA analysis on drug effect within ADHD boys for the Failed inhibition-Go trials contrast. Axial sections showing the repeated measures ANOVA results for the drug effect within ADHD patients (Placebo, MPH, ATX). Talairach z-coordinates are

indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

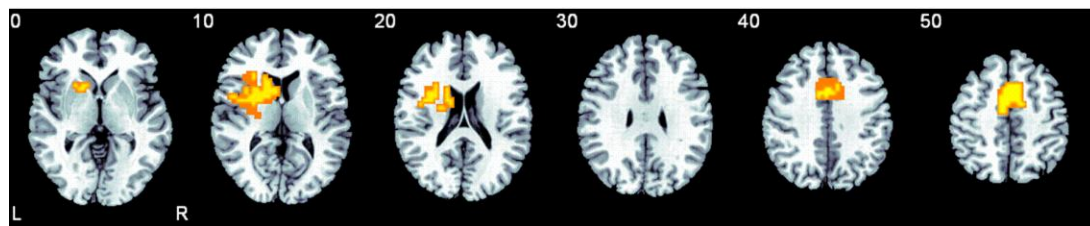
6.3.6. Inverse contrast of Go – Successful Stop trials and Go – Failed Stop Trials

No differences were observed between controls and patients under placebo or under ATX for the inverse contrast of Go-Successful Stop trials. However, patients under MPH showed enhanced activation in left insula/VLPFC and premotor cortex, reaching into caudate, putamen and globus pallidus (187 voxels, peak Talairach coordinates (x;y;z): -25; 19; 13; BA 45/6; $p < 0.006$), and in ACC/SMA (162 voxels, peak Talairach coordinates (x;y;z): 4; 11; 43; BA 6/24/32; $p < 0.003$) (Figure 6.8). The same regions were enhanced during observed in the inverse contrast of Go – Failed Stop trials, although in this case the cluster in the ACC/SMA reached also into the right striatum (262 voxels, peak Talairach coordinates (x;y;z): 4; 11; 43; BA 24/32/6; $p < 0.002$) and the cluster in left basal ganglia and premotor regions showed a bigger cluster size (331 voxels, peak Talairach coordinates (x;y;z): -25;-4; 10; BA 45/4/6; $p < 0.001$) (Figure 6.8). There were no significant correlations between brain activation and performance. In the Go - Successful Stop trials contrast, Friedman tests showed significant differences between brain activation within patients under each drug condition in the basal ganglia/ left premotor-VLPFC cluster (BOLD Placebo: -0.001; BOLD MPH: -0.031; BOLD ATX: 0.001; χ^2 (2, N=19) = 6.42, $p < 0.04$), due to the significantly enhanced activation during correct motor responses to go trials under MPH relative to that under placebo ($p < 0.002$) and ATX ($p < 0.033$). Similarly, Friedman tests showed significant differences SMA/ACC cluster (BOLD Placebo: 0.035; BOLD MPH: -0.023; BOLD ATX: 0.024; χ^2 (2, N=19) = 15.47, $p < 0.001$), due to the significant differences between MPH and Placebo ($p < 0.001$) and between MPH and ATX (0.004).

Similarly, in the contrast of Go - Failed Stop, Friedman tests showed significant differences between the three drug conditions in the cluster of basal ganglia/premotor activation (BOLD Placebo: < -0.001 ; BOLD MPH: -0.025; BOLD ATX: -0.005; χ^2 (2, N=19) = 9.79, $p < 0.007$), due to significantly enhanced activation during motor responses under MPH relative to placebo ($p < 0.004$) and, at a trend level, to ATX ($p < 0.059$). Significant differences were also observed between activation under the three drug conditions in the SMA/ACC cluster (BOLD Placebo: 0.014;

BOLD MPH: -0.026; BOLD ATX: 0.009; χ^2 (2, N=19) = 14.00, $p < 0.001$), due to the enhanced activation during go responses under MPH relative to Placebo ($p < 0.001$) and ATX ($p < 0.003$).

Go – Successful inhibition trials ADHD MPH > C



Go – Failed inhibition trials ADHD MPH > C

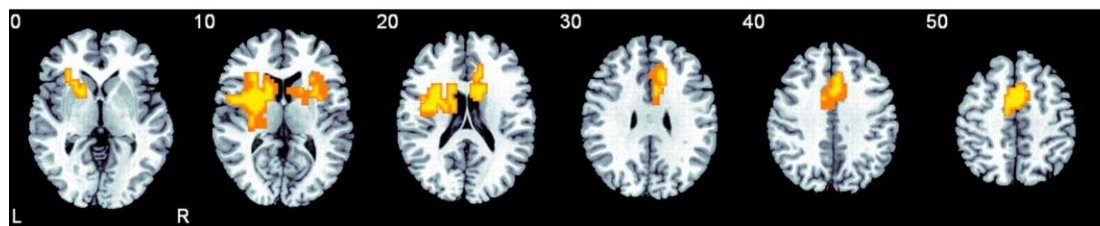


Figure 6.8. Between-group ANOVA comparison between healthy control boys and boys with ADHD under Methylphenidate for the contrasts of a) Go – Successful inhibition trials and b) Go – Failed inhibition trials. Axial sections showing the ANOVA between-group difference effects in brain activation between healthy control boys and boys with ADHD under MPH. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

6.4. Discussion

The study shows both shared and drug-specific normalisation and upregulation effects on inhibitory brain regions in ADHD patients. ADHD relative to control boys showed no performance deficits but significantly improved in their inhibitory capacity relative to controls under MPH. During the main contrast of successful inhibition, patients under placebo had reduced activation in left and right VLPFC, left MTG, and right cerebellum. Relative to controls, both drugs showed shared moderate

normalisation effects in left VLPFC activation, while only MPH showed drug-specific normalisation effects on the key inhibitory region of right VLPFC.

The underactivation in ADHD patients in key areas of motor response inhibition in right and left VLPFC as well as in parieto-temporal regions is in line with previous findings (Cubillo et al., 2012; Epstein et al., 2007; Rubia, 2011; Rubia, Cubillo, et al., 2010; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005). While right VLPFC is a key area of inhibition (Chambers et al., 2009; Rubia, Smith, et al., 2003) left VLPFC forms also part of the inhibition network (Nee et al., 2007; Swick et al., 2008), but has been suggested to mediate performance monitoring (Derrfuss et al., 2005; Stevens, Kiehl, Pearlson, & Calhoun, 2009). Although less commonly reported, the cerebellum is correlated with SSRT in the Stop task in healthy adolescents and adults (Rubia, Smith, Taylor, et al., 2007), which was also observed in this study. The finding replicates a previous finding of cerebellar underactivation during the Stop task in ADHD children (Rubia, Halari, Mohammad, et al., 2011). The enhanced activation in patients under placebo relative to controls in right STG-putamen and left cerebellum/occipital cortex was likely compensatory, as suggested by the negative association of STG-putamen activation with inhibitory capacity and with the (reduced) left VLPFC activation. This compensatory enhanced activation in STG, part of the inferior frontal-superior temporal junction that mediates inhibition (Chambers et al., 2009; Rubia, Smith, et al.; Rubia, Smith, Taylor, et al., 2007) may have prevented patients from inhibitory impairment in the task.

Only MPH significantly normalised the right VLPFC underactivation suggesting a drug-specific effect on normalising the key inhibition area, the right VLPFC. Further normalisation effects were observed in the cerebellum, which, however, in exploratory post-hoc analyses showed to be significant for MPH only. The findings extend previous normalisation and upregulation findings with MPH in fronto-striato-cerebellar inhibitory network during inhibition tasks in children with ADHD (Epstein et al., 2007; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998). This is furthermore in line with a recent neuropsychological study, which showed that only acute dose challenge of MPH and not of ATX improved performance during the Stop task in healthy adults (Nandam et al., 2011). However, it is of note here that the normalisation effects of ATX on right VLPFC and cerebellar activation were not absent, but moderate. Considering that ATX typically takes longer to show significant behavioural effects than MPH

(Montoya et al., 2009), longer-term administration may have resulted in significant effect size differences relative to placebo for the below-threshold normalised right VLPFC and cerebellar underactivation. Future studies will have to compare long-term administration of both drugs to elucidate this question. In healthy adults, a comparatively lower dose of ATX has shown upregulation effects of ATX on right IFC activation (Chamberlain et al., 2009). Whether these effects would become significant at different doses of ATX or after repeated administration should be further studied.

The shared moderate normalisation findings of MPH and ATX in left VLPFC underactivation are interesting as these findings extend, for the first time, previous findings of upregulation of right (Chamberlain et al., 2009) and bilateral VLPFC (Graf et al., 2011) with ATX in healthy adults during motor inhibition tasks to medication-naïve children with ADHD. Although the left VLPFC is involved in motor inhibition processes (Nee et al., 2007; Swick et al., 2008), left lateralised effects may suggest stronger effects of ATX on performance monitoring (Derrfuss et al., 2005; Stevens et al., 2009) rather than inhibition per se. Furthermore, the lack of association between inhibitory measures (SSRT) and activation in left VLPFC suggests the shared normalised effects of both drugs may be due to improved performance monitoring processes.

Patients under placebo showed enhanced activation compared to controls in two clusters, in the STG-putamen and a second one comprising the left occipital/posterior cerebellum. Their potentially compensatory role was furthermore supported by their association with inhibitory performance measures as also by the association between enhanced activation in STG-putamen and the reduced activation in left VLPFC. We observed shared and differential effects with regards to these two clusters of activation differences.

Both drugs showed shared normalization effects in the right STG-putamen cluster. The STG is anatomically connected to caudate and putamen (Yeterian & Pandya, 1998), and involved in selective visuo-spatial attention (Hopfinger, Buonocore, & Mangun, 2000) and spatial awareness (Karnath, Ferber, & Himmelbach, 2001). Enhanced activation in insula and putamen in medication-naïve children with ADHD, as well as its downregulation after stimulant administration has been previously reported during different cognitive tasks (Konrad et al., 2007; Rubia,

Halari, Christakou, et al., 2009), therefore this study shows that this finding is not task-specific and also extends to the non-stimulant ATX.

Differential effects were observed with regards to the second cluster of enhanced activation in patients under placebo relative to controls in left occipital/posterior cerebellum. Previous studies have shown enhanced activation in cerebellar and occipital regions in children (Rubia, Smith, et al., 2009) and adults with ADHD (Cubillo et al., 2012). Furthermore, MPH has shown to enhance/normalise activation in cerebellum and occipital regions in children with ADHD (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009). ATX completely normalised the enhanced activation in this cluster however, under MPH the enhanced activation in left occipital/cerebellar regions persisted, and reached dorsal regions of the PCC and to the left precuneus. The PCC and precuneus are typically involved in attention allocation to salient stimuli and performance monitoring processes (Cavanna & Trimble, 2006; Mesulam et al., 2001; Mohanty et al., 2008; Rubia, Smith, Taylor, et al., 2007; Sack, 2009). Furthermore, the association between the enhanced activation in left occipital/posterior cerebellum and inhibitory performance measures suggests its potential compensatory role.

Interestingly, MPH in addition, showed a drug-specific upregulation effect during the executive Go process of the task, both in the within-subjects and in the between-group comparisons, in key regions for response selection and motor execution in ACC/SMA, left premotor cortex and basal ganglia (Haber, 2003; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). Together, the findings thus suggest that MPH upregulates and normalises right-lateralised VLPFC-cerebellar motor inhibition networks as well as medial fronto-striatal circuits of motor response execution.

During failed inhibition, patients under placebo relative to controls showed underactivation in regions mostly overlapping those observed in the successful inhibition contrast, in line with the evidence that suggests that inhibition-related networks are active to a very similar degree during both conditions (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2010). The only exception was the reduced activation in the thalamus, which may be associated to its relevance during error detection and feedback processing (Li, Yan, Chao, et al., 2008; Ullsperger & von Cramon, 2003).

During failed inhibitory trials both drugs normalised right VLPFC, thalamic and temporo-parietal regions which were underactivated in patients under placebo compared with controls. However, as in the successful inhibition contrast, the normalising effects were only significant for MPH in the right VLPFC, while shared effects were observed for both drugs on temporo-parietal regions. These findings suggest significant normalisation effects of both drugs in temporo-parietal regions involved in the detection of salient events, i.e. failed inhibitory trials during the task (Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Rubia, Hyde, et al., 2010; Stevens, Skudlarski, Gatenby, & Gore, 2000). On the other hand, only the effects of MPH were strong enough to “normalise” the right VLPFC underactivation in patients under placebo relative to controls, while the effects of ATX on this region are moderate.

While the inhibitory performance of the patients under MPH (as measured by the main inhibitory index of the task, the SSRT) was numerically better than when under Placebo or ATX, it did not reach significance. However, MPH significantly improved inhibitory performance in ADHD boys relative to that of the healthy control group, suggesting it had a positive impact on SSRT. The normalisation effects of MPH on key inhibitory activation areas right VLPFC and cerebellum after a single dose of Methylphenidate may have accounted for their relative improvement on inhibitory performance compared to healthy controls.

Nevertheless, it should be noted that the SSRT of the group of patients was not significantly different from that of controls during the placebo condition, which is not in line with the findings from previous neuropsychological studies, which, as reviewed in chapter 1, have shown longer SSRTs in ADHD patients relative to healthy controls (Alderson et al., 2007; de Zeeuw et al., 2008; Epstein, Langberg, et al., 2011; Lee et al., 2008; Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Martel et al., 2007; Nigg et al., 2005; Rommelse et al., 2008; Rubia, Smith, et al., 2007a; Willcutt et al., 2005). A number of factors may have contributed to the performance profile observed in this study. Case-control fMRI studies on cognitive functions that cannot be mastered well by patients are confounded by differences in performance, which makes necessary the use of easier task designs than those used in neuropsychological studies. Furthermore, there are the restrictions to the design of fast event-related fMRI tasks: target trials cannot be consecutive and need to be separated sufficiently from non-target trials (at least 3 trials) so as to allow for separability of the haemodynamic response. This resulted in Stop trials being less randomly

interspersed with Go trials than in typical neuropsychological designs of the task, making the Stop trials slightly more predictable (and consequently, easier) than in offline versions. A key factor may furthermore have been that the children with ADHD performed the task on three occasions, while the healthy control group only performed the task once. Although there were no significant effects of order of administration of the drugs within patients, the small numbers in each subgroup do not allow to totally exclude a potential effect of learning or the presence of potential sequence effects, and therefore need to be taken into account. However, although this may have contributed to the non-significant differences in SSRT, it seems unlikely to solely explain the significant difference between healthy controls and patients under MPH. While SSRTs were (non-significantly) longer in patients under placebo when this was administered during the first scanning session relative to the second or third sessions, this was not the case when patients were under MPH or ATX.

Some of the characteristics of the sample may have also led to a less impaired sample than those typically recruited during neuropsychological studies. Due to movement artefacts, fMRI studies of ADHD tend to recruit milder cases, which, together with the reduced number of subjects compared the larger sample sizes typically recruited in neuropsychological studies, may have reduced the power of the present study to reliably identify performance differences between the groups. Furthermore, the mean age of the subjects in neuropsychological studies is 8-10 years of age, while this study recruited an older sample (10 to 17 years of age). Given that in a significant proportion of cases inhibitory impairments tend to disappear with age, no longer presenting those in adulthood, it may be that the older age range with respect to that typical in neuropsychological studies may also have contributed to the performance observed in this study. In addition, some neuropsychological studies have reported no deficits in inhibitory function as measured by the SSRT in children with ADHD (i.e. Kuntsi et al., 2001; Manassis, Tannock, & Barbosa, 2000; Scheres et al., 2001), and recent studies have shown that only a proportion of children with ADHD show performance impairments during inhibitory measures (Nigg et al., 2005; Sonuga-Barke et al., 2010). Most importantly, most fMRI studies in older ADHD adolescents have not shown any deficits in SSRT, likely for the above mentioned reasons (Rubia, Halari, Mohammad, et al., 2011; Rubia, Cubillo, et al., 2010; Rubia et al., 2008; Rubia, Overmeyer, et al., 1999; Rubia et al., 2005).

In conclusion, the fMRI adaptation which makes the task easier than those versions used in neuropsychological studies, the older and potentially less severe ADHD group recruited relative to those patients typically recruited in neuropsychological studies and the repeated performance of the task by the group of children with ADHD relative to the single performance of controls may have contributed to the unusual performance profile observed in the present study of no SSRT deficits in ADHD patients under placebo.

A strength of this study is the double-blind, placebo-controlled crossover design in exclusively medication-naïve boys with combined type ADHD, thus testing a homogeneous sample and avoiding the potential confound of previous stimulant medication history, known to confound brain structure and function deficits (Frodin & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011). A limitation is that ADHD boys performed the task three times, while, for financial and ethical reasons, controls were scanned only once. Although we could not directly measure the practice effects in the between group analyses, given that there were no differences in the within group analysis, we assume that they were unlikely to have contributed to performance or brain activation differences between patients and controls. However, such assumption must be made with caution, as we could only test for potential order effects within subjects. Even then, this was conducted in a very small sample, and therefore the power to detect potential order effects is severely reduced. Furthermore, given the reduced number of participants on each condition, it was not possible to test for potential sequence effects derived from the randomisation order. That means that the administration of the drug conditions in a determined randomization order may have enhanced or reduced their effects. Further studies with sufficiently large samples should be conducted to rule out this possibility. In addition, the wider age range in the age of the healthy control group relative to the ADHD boys may have affected the results, potentially making more pronounced the between-groups differences in a disorder that has shown to be associated with neurodevelopmental delay (Rubia, 2007; Shaw et al., 2007; Shaw et al., 2012). Therefore, future studies should ideally include more closely age-matched groups.

Another limitation is the single dose administration. While MPH has immediate effects on behaviour (Greenhill et al., 2001), ATX reaches its maximum behavioural efficacy at about 12 weeks (Montoya et al., 2009). Consequently, a single dose comparison may have favoured MPH. The investigation of acute mechanisms of

action, however, is a first step towards improving our understanding of drug-specific effects on brain activation and cognition, and has the advantage of avoiding potential confounds of long-term treatment such as symptomatic improvement, side effects or chronic effects on brain activation. However, the presence of significant effects for ATX on left VLPFC and of moderate effects on right VLPFC and cerebellar regions suggest it modulates activation on key inhibitory regions, which may be stronger at different doses or after prolonged administration. Therefore, future studies should compare different doses and long-term effects of both drugs on brain activation after reaching maximum clinical efficacy.

To summarise, the findings show shared effects of both drugs of normalising left VLPFC activation deficits in ADHD patients. MPH, however, had drug-specific normalisation effects in right VLPFC. In addition MPH not only upregulated fronto-cerebellar areas of inhibitory control but also fronto-striatal regions mediating the executive Go process of the task.

CHAPTER 7: DRUG-SPECIFIC FRONTAL EFFECTS OF ATOMOXETINE AND METHYLPHENIDATE IN ADHD BOYS DURING WORKING MEMORY

7.1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterised by age-inappropriate symptoms of inattention, impulsivity and hyperactivity (American Psychiatric Association, 2000). One of the key neuropsychological deficits is WM (Martinussen et al., 2005), underpinned by fMRI evidence for reduced fronto-striatal and temporo-parietal activation (Kobel et al., 2009; Silk et al., 2005; Vance et al., 2007).

The stimulant MPH and the non-stimulant ATX are the most commonly prescribed pharmacological treatments for ADHD, showing comparable efficacy in 65-70% of cases (Hazell et al., 2010). However, the drug-specific mechanisms of action on brain function in ADHD patients are unknown.

MPH blocks DAT in the striatum (Volkow, Wang, Fowler, Gatley, et al., 1998) and NET in NET-rich regions including prefrontal regions, where it enhances both catecholamines (Hannestad et al., 2010). ATX is a selective pre-synaptic NET blocker affecting NE and DA in prefrontal cortex (Bymaster et al., 2002) and NE in thalamus, locus coeruleus and cerebellum, with minimal striatal effects (Gallezot et al., 2011).

A single dose of MPH in ADHD children has shown to upregulate and/or normalise fronto-striatal, temporo-parietal and cerebellar regions during cognitive control tasks (Epstein et al., 2007; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009; Shafritz et al., 2004; Vaidya et al., 1998).

Few fMRI studies, however, have tested for MPH effects on WM in ADHD children, with inconsistent results. Thus, MPH normalised IFC, MFC, and striatal underactivation in ADHD children off-MPH compared to controls (Prehn-Kristensen et al., 2011) and upregulated activation and functional integration in fronto-parietal WM networks (Wong & Stevens, 2012). However, a single dose of MPH downregulated MFC and parietal activation during WM in female ADHD (Sheridan et al., 2010) but with no effects in ADHD boys (Kobel et al., 2009). These studies,

however, did not include a placebo condition, had small sample sizes and recruited patients with a previous history of stimulant medication, shown to have effects on both brain activation and structure (Frodl & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011).

No fMRI study has as yet investigated the effects of ATX on brain activation in ADHD patients during any cognitive function, or compared its effects to those of MPH. In healthy adults, acute ATX administration upregulates IFC and STG during inhibitory tasks (Chamberlain et al., 2009; Graf et al., 2011), and using multivariate pattern recognition analyses ATX had relatively stronger deactivation effects on the DMN while MPH has relatively stronger upregulating effects on WM networks (Marquand et al., 2011).

We therefore conducted a randomised, double-blind, placebo-controlled, cross-over pharmacological fMRI study to test for drug-specific effects of a single clinical dose of either MPH or ATX on brain activation of medication-naïve boys with ADHD during a verbal WM task. The focus on single rather than long-term drug effects on neurofunctional mechanisms avoids potential confounds including side effects, symptomatic improvement or chronic effects on brain activation. We furthermore compared brain activation during the WM task in patients under each drug condition with that of age-matched healthy controls to test for potential drug normalisation effects. Based on previous fMRI studies of WM in ADHD children (Prehn-Kristensen et al., 2011), we hypothesised that ADHD boys would show underactivation relative to controls in DLPFC and parietal regions. Furthermore, based on previous findings of upregulation of MPH on brain activation in ADHD (Prehn-Kristensen et al., 2011; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009; Shafritz et al., 2004; Vaidya et al., 1998) and of ATX on brain activation in healthy adults (Chamberlain et al., 2009; Graf et al., 2011), we hypothesized that both drugs would upregulate and normalise the reduced activation in lateral PFC and that MPH would additionally enhance basal ganglia activation.

7.2. Methods

7.2.1. Subjects

Thirty medication-naïve right-handed boys between 10-17 years with a clinical diagnosis of ADHD (DSM-IV-TR)(American Psychiatric Association, 2000) were recruited through clinics. Patients had clinical diagnosis of ADHD, inattentive/hyperactive-impulsive combined subtype, as assessed by an experienced child psychiatrist using the standardized Maudsley diagnostic interview that assesses ADHD according to DSM-IV-TR criteria (Goldberg & Murray, 2002). A multidisciplinary clinical team participated in the assessment, which typically included information from semi-structured clinical assessment interviews with parents/carers, questionnaires from parents and teachers, school reports, developmental history, cognitive assessments and behavioural observation of the child. The presence of learning disability was concluded from the information provided by parents and school during the clinical and cognitive assessments, or by the presence of significant discrepancies between verbal and performance IQ subscores, which is considered as an indicator of potential learning difficulties.

ADHD boys scored above clinical threshold for hyperactive-impulsive/inattentive symptoms on the SDQ (Goodman & Scott, 1999), the CPRS-R (Conners et al., 1998), and below clinical threshold on the SCQ (Rutter et al., 2003)(Table 7.1). Patients were scanned in a double-blind, placebo-controlled, crossover design. On each scanning session, they received a single dose of either placebo (Vitamin C, 50mg), MPH (Equasym, 0.3mg/kg, range 5–20mg) or ATX (Strattera, 1mg/kg, range 16-66mg), in a pseudo-randomized order, and remained medication-free between scans. Dosages were determined following NICE guidelines of clinical efficacious dosages with minimal side effects at the time of the study (National Institute for Health and Clinical Excellence, 2008). Based on pharmacokinetic evidence, both medications were administered 1.5 hours before the scan to allow for maximum absorption (Chan et al., 1983; Witcher et al., 2003). The same or similar dosages and time lapses between drug administration and scan have shown to be sufficient to observe changes in brain activation and performance in ADHD patients (MPH)(Lijffijt et al., 2006; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011) and healthy controls (ATX)(Chamberlain et al.,

2007; Chamberlain et al., 2009). All three medications were over-encapsulated using the same capsules by the pharmacist.

Twenty-one right-handed healthy boys (between 10-17 years) were recruited through advertisement in the same geographical South London area. They scored below clinical cut-offs for the SDQ, SCQ and CPRS-R (Table 7.1.). They were scanned once, unmedicated.

Exclusion criteria for all participants were IQ<70 on the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999), history of substance abuse or neurological deficits, learning disability, reading, speech or language disorder, as well as the presence of psychiatric disorders (except for ADHD and conduct disorder (CD)/oppositional defiant disorder (ODD) in the ADHD group). When parental reports for potential participants were suggestive of the presence of such difficulties, questions addressing each of the criteria for CD/ODD were included in the semi-structured interviews. Thus, despite the fact that the mean score in the ADHD group for oppositional problems in the CPRS-R and behavioural difficulties in the SDQ scales were above clinical cut-offs (Table 7.1), only two cases received the formal diagnosis of ODD/CD.

Eleven participants (1 control, 10 ADHD boys) were excluded due to: above clinical threshold on the CPRS-R score in one control subject, IQ <70 (N=1), excessive motion parameters (>3mm)(N=1), neurological abnormalities detected at the scan (N=1), technical problems that led to loss of data (N=2), inability to tolerate the scanning situation (N=4) or braces (N=1). Thus, the final sample consisted of 20 healthy control boys and 20 medication-naïve children with ADHD (Table 7.1).

Table 7.1. Sample characteristics for healthy control boys and patients with ADHD.

Variables	Controls (20) Mean (SD)	ADHD (20) Mean (SD)
Age (years, months)	13y, 8m (2y, 5m)	13y, 0m (1y, 7m)
Age range (years, months)	10y,3m- 17y, 8m	10y, 1m-15y, 6m
IQ	114 (11)	91 (11)
SDQ Hyperactive-impulsive/ Inattentive Subscale	2(2)	8 (2)
SDQ Total score	4 (4)	22 (7)
SDQ Emotional difficulties subscale	1 (2)	4 (3)
SDQ Behavioural difficulties subscale	0 (1)	6 (3)
SDQ Getting along difficulties subscale	1 (1)	3 (3)
SDQ Kind and helpful behaviours subscale	9 (2)	6 (2)
SCQ Total	1 (1)	9 (5)
CPRS-R Total T score	44 (5)	78 (11)
CPRS-R oppositional T score	43 (4)	75 (12)
CPRS-R Cognitive/ inattention problems T Score	45 (4)	69 (9)
CPRS-R hyperactivity T score	46 (4)	79 (14)
CPRS-R anxious/shy T score	49 (9)	60 (16)
CPRS-R Perfectionism T score	44 (4)	56 (16)
CPRS-R social problems T score	47 (3)	59 (13)
CPRS-R Psychosomatic T score	48 (7)	60 (15)
CPRS-R Global Index: restless impulsive T score	44 (3)	76 (12)
CPRS-R Global Index: emotional liability T score	44 (5)	72 (14)

Note: SDQ=Strengths and Difficulties Questionnaire; CPRS-R: Conners' Parent Rating Scale; SD= Standard Deviation

One-way analyses of variance (ANOVAs) showed no between-group differences for age ($F(1,38)=0.88$; $p<0.35$) but for IQ ($F(1,38)=41$; $p<0.001$) (Table 7.1.). Low IQ is associated with ADHD (Bridgett & Walker, 2006). WM tasks such as the N-Back task have shown to be closely associated with IQ measures, with additional indirect evidence suggesting they may share a common neurological base, with the DLPFC being a key region (Conway et al., 2003). WM is indeed one of the factors obtained in typical tests of general intelligence such as the Wechsler Intelligence Scale for Children (4th version) (WISC-IV) (Wechsler, 2004). Therefore, covarying for IQ during this task would indeed mean covarying for any differences in WM that may exist between the groups. Seven of the ADHD participants had been assessed using the WISC-IV. Therefore, all analyses were conducted without IQ as a covariate. However, in order to test for potential effects of outliers subjects with an IQ more than 2 SD above or below average, we repeated the analyses excluding these outliers ($N=4$ in each group).

Participants were paid £50 for each scanning session. Parental/child informed consent/assent and approval from the local Ethical Committee were obtained.

7.2.2. Paradigm: WM task (N-Back)

Subjects practiced the task once before scanning. The 6-minute block design WM task consists of 4 conditions. During “1-back”, “2-Back” and “3-Back” conditions, subjects are presented with series of letters (A-Z) and must respond with their right thumb using a button box whenever the letter presented is the same as one, two or three before it, respectively (e.g. 2-Back:B/J/A/J) (Figure 7.1.). In the baseline vigilance “0-Back” condition, subjects must respond to each X that appears on the screen. The task consists of 12 randomized blocks. At the beginning of each block, written instructions (e.g. “2-Back”, duration: 3 secs) are shown as to which condition is next (0-Back;1-Back;2-Back;3-Back). In each of the blocks (duration: 31 secs), only one condition is presented, and contains fifteen stimuli: three targets and twelve non-targets. Each condition is presented three times.

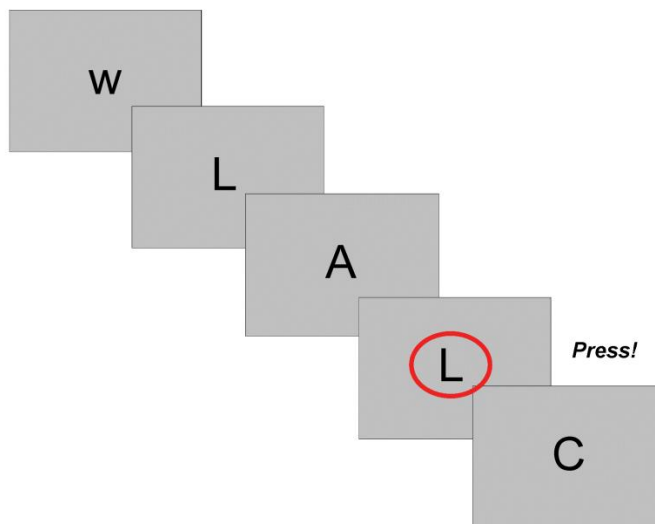


Figure 7.1. Schematic figure for the N-Back task.

The 6 minutes working memory (WM) task consists of 4 different conditions. In the control condition “It is X?” the subject is presented to series of letters, and the subject has to press for every X that appears on the screen. In the conditions “1-back”, “2-back” and “3-back”, the subject has to press the button whenever the letter presented is the same as one, two or three before it, respectively. Image corresponds to the 2-Back condition.

7.2.3. fMRI acquisition and analyses

Gradient-echo echoplanar MR imaging (EPI) data were acquired on a GE Signa 3T Horizon HDx system (General Electric, Milwaukee, WI, USA) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King’s College London, UK. A semi-automated quality control procedure ensured consistent image quality (Simmons et al., 1999). A quadrature birdcage head coil was used for RF transmission and reception. In each of 39 non-contiguous planes parallel to the anterior-posterior commissure line, 186 T₂*-weighted MR images depicting BOLD (Blood Oxygen Level Dependent) contrast covering the whole brain were acquired with TE=30ms, TR=2s, flip angle=75°, in-plane resolution=3mm, slice thickness=3.5mm, slice-skip=0.5mm. This EPI dataset provided complete brain coverage.

Blocked fMRI data were acquired in randomized block presentation, and analysed using the non-parametric XBAM software (Brain Image Analysis Unit,

2011; Brammer et al., 1997; Bullmore et al., 2001; Bullmore, Brammer, et al., 1999). XBAM uses median statistics to control for outlier effects and permutation rather than normal theory-based inference. Furthermore, the most common test statistic is computed by standardising for individual difference in residual noise before embarking on second level, multi-subject testing using robust permutation-based methods. This allows a mixed effects approach to analysis recommended for fMRI (Thirion et al., 2007).

fMRI data were first processed to minimise motion related artifacts (Bullmore, Brammer, et al., 1999). A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x y and z axes) and translations (in x y and z) that maximised the correlation between the image intensities of the volume in question and the template (rigid body registration). Following realignment, data were then smoothed using a Gaussian filter (FWHM, 7.2mm) to improve the signal to noise characteristics of the images.

After preprocessing, time series analysis for each individual subject was based on a wavelet-based data resampling method for functional MRI data (Bullmore et al., 2001; Bullmore, Brammer, et al., 1999). We first convolved each experimental condition (1-Back; 2-Back; 3-Back; contrasted with 0-Back) with two Poisson model functions (peaking at 4s and 8s) after motion correction, global detrending and spin-excitation history correction. We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ-ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ-ratio for each subject, which were combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial

correlation structure in the data. After first-level analysis, the individual statistical maps were then normalised into Talairach standard space (Bullmore et al., 2001).

A group activation map was then produced for each of the experimental conditions (1-Back; 2-Back; 3-Back) by calculating the median SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). The voxel-level threshold was first set to $p < 0.05$ to give maximum sensitivity and to avoid type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters such that the final expected number of type I error clusters was < 1 per whole brain. Cluster mass rather than a cluster extent threshold was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore, Suckling, et al., 1999).

In both ANOVA designs, we used randomization-based tests for voxel or cluster-wise differences (Bullmore, Suckling, et al., 1999). Less than 1 false activated cluster was expected at a p -value of $p < 0.05$ for voxel and $p < 0.01$ for cluster comparisons. Thus, an expected cluster-level type I error rate of < 1 per brain was achieved by first applying a voxel-level threshold of $p < 0.05$ followed by thresholding the mass of the 3D clusters formed from the voxels that survived this initial step at a cluster-level threshold of $p < 0.01$. The cluster level threshold of $p < 0.01$, was therefore not applied to the whole brain (which would be lenient) but rather to the data previously thresholded at a voxel-wise level of $p < 0.05$. The necessary combination of voxel and cluster level thresholds is not assumed from theory but rather determined by direct permutation for each data set. This combined voxel/cluster tests coupled with permutation testing allow for type I error control at the cluster level (Bullmore, Brammer, et al., 1999; Bullmore, Suckling, et al., 1999). For each analysis, < 1 false positive 3D cluster per map were expected at a p -value of < 0.05 at the voxel-level and < 0.01 at the cluster-level. In large connected clusters, we identified local maxima that were farther apart than the upper bound of the likely Talairach mapping error (3 voxel radius: 10 mm) (Thirion et al., 2007). Voxels were then assigned to the nearest local maximum with a statistic value that exceeded that of the voxels.

For between-group comparisons, a 2x3 split-plot design ANOVA (groups: controls, patients; WM-load: 1-Back, 2-Back, 3-Back, each separately contrasted with

0-Back) was conducted. For within-group comparisons, a 3x3 factorial design repeated measures ANOVA (drug condition: placebo, MPH, ATX; WM-load: 1-Back, 2-Back, 3-Back, separately contrasted with 0-Back) was conducted. Statistical measures of BOLD response were extracted for each participant in each of the clusters of activation differences for each of the three contrasts, and post-hoc analyses were conducted to clarify the direction of the differences. Within patients, repeated measures ANOVAs on the extracted BOLD response measures were conducted to test for potential order effects.

7.2.4. Performance analysis

For the main performance measures of errors and MRT in the case-control comparisons, three repeated measures ANOVAs (controls versus ADHD under placebo; controls versus ADHD under MPH and controls versus ADHD under ATX) were conducted with WM-load as the within-subjects factor and group as the between-subjects factor. Within patients, repeated measures ANOVAs were conducted with drug condition (Placebo, MPH, ATX) and WM-load (1-Back, 2-Back, 3-Back) as within-subject factors. Repeated measures ANOVAs were conducted within patients to test for potential order effects.

7.3. Results

7.3.1. Performance data

Significant WM-load effects were observed for patients in errors ($F(2,38)=34$, $p<0.001$) and MRT ($F(2,38)=18$, $p<0.001$), and also in controls (Errors: $F(2,38)=26$, $p<0.001$; MRT: $F(2,38)=13$, $p<0.001$).

In case-control comparisons, no group effects were found. However, there was a significant interaction between WM-load and group in the number of errors only when comparing controls with patients under placebo ($F(2,76)=3$; $p<0.037$), which was due to patients making less errors during 1-Back but more errors during 2- and 3-Back than healthy controls (Table 7.2). There was also an interaction effect between WM-load and group in MRT when healthy controls were compared to patients under placebo ($F(2,76)=6$, $p<0.005$) or under ATX ($F(2,76)=5$, $p<0.01$), both due to patients

showing similar MRT to controls during 1-Back, but being slower than controls during 2-Back, and faster during 3-Back (Table 7.2).

Within patients, no drug condition, WM-load by drug condition interaction or order effects on performance variables were detected.

No other group, group by WM-load interaction or drug order effects were observed.

Table 7.2. Performance data for 20 healthy control boys and 20 boys with ADHD under each medication condition

Performance Variable	Task condition	Controls Mean (SD)	ADHD Placebo Mean (SD)	ADHD MPH Mean (SD)	ADHD ATX Mean (SD)
Percentage Errors	1-Back	8 (17)	3 (6)	2 (6)	5 (16)
	2-Back	13 (22)	23 (26)	18 (25)	19 (26)
	3-Back	32 (21)	40 (28)	34 (24)	37 (27)
Mean reaction time (milliseconds)	1-Back	605 (154)	616 (153)	602 (98)	594 (153)
	2-Back	623 (127)	685 (182)	677 (155)	704 (208)
	3-Back	766 (166)	690 (151)	743 (204)	706 (174)

Note: ATX = Atomoxetine; MPH = Methylphenidate

7.3.2. Brain activation

7.3.2.1. Motion

Multivariate ANOVA showed no significant group differences between controls and ADHD patients under each drug condition in the extent of mean rotation and translation movement parameters in the 3-dimensional Euclidean space ($F(6,152)=1;p=0.43$).

7.3.2.2. Within-groups brain activation

During the easier condition (1-Back), controls showed activation in right DLPFC, in left IFC extending to premotor areas, and in bilateral parietal regions. During 2-Back, activation was observed in the group of healthy controls in bilateral DLPFC, extending to inferior prefrontal cortex IFC, bilateral thalamus, STG, IPL,

precuneus and occipital regions. Additional activation was observed during the more difficult condition (3-Back) in the left caudate body extending to mid-cingulate gyrus, as well as in the dorsal ACC extending to the SMA (Table 7.3, Figure 7.2).

Boys with ADHD under placebo showed activation during the easier 1-Back condition in bilateral medial frontal regions, in left IFC, striatum bilaterally, and in right IPL. During the 2-Back condition, children with ADHD showed activation in bilateral IFC, MFC and SFC, ACC, striatum, precuneus, IPL and SPL, as well as in the right lingual cortex. These regions were also activated during the more difficult 3-Back condition of the task, with bigger cluster sizes especially in the striatum, and with additional activation in the cerebellar vermis, subthalamic nuclei and in left parahippocampal gyrus (Table 7.3, Figure 7.2).

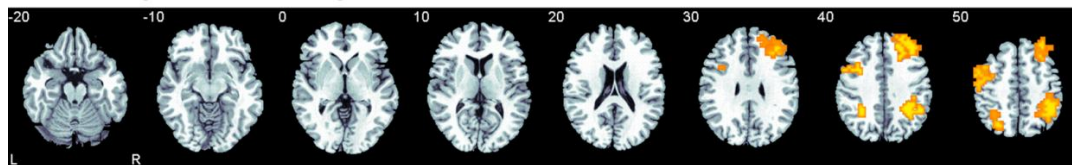
After acute MPH administration, boys with ADHD during the easier condition (1-Back) showed activation left IFC and MFC, in bilateral ITG and MTG, and in right parietal regions as well as in cerebellar vermis. During 2-Back, boys with ADHD after MPH showed activation in bilateral IFC, MFC, SFC brain regions, precentral cortices, striatum, thalamus, insula, dorsal ACC, precuneus, IPL, subthalamic nuclei and the cerebellar vermis. During the more difficult condition (3-Back), activation was observed in the same brain regions, but extending further into the cerebellum and subthalamic nuclei, and with less activation in frontal and striatal regions (Table 7.3, Figure 7.2).

Boys with ADHD under a single dose of ATX showed activation during 1-Back in bilateral IFC, striatum, ACC, thalamus, MTG, as well as in right parietal regions and cerebellar vermis. During the 2-Back condition, children with ADHD under ATX showed activation in bilateral IFC, MFC and SFC, ACC and SMA, striatum, thalamus, insula, temporo-parietal regions, cuneus, precuneus and subthalamic nuclei. The same regions were activated during the difficult condition, but more extensively, with the exception of temporal regions that were no longer observed, and with additional activation in the cerebellar vermis (Table 7.3, Figure 7.2).

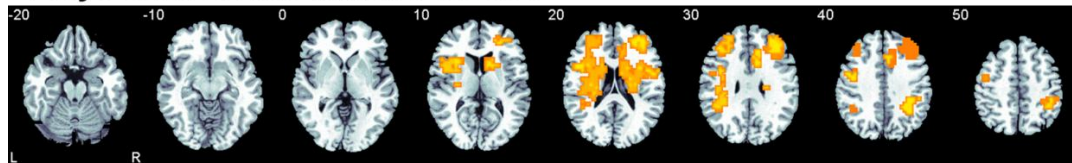
Within-group activations for the three task conditions

a) 1-Back

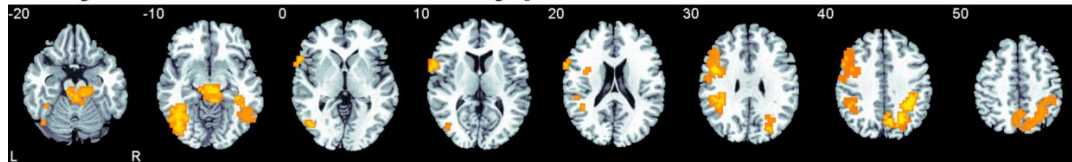
Healthy control boys



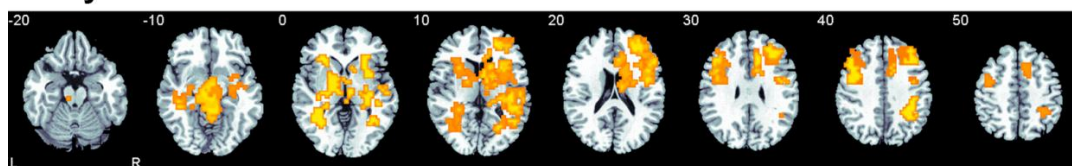
Boys with ADHD under Placebo



Boys with ADHD under Methylphenidate

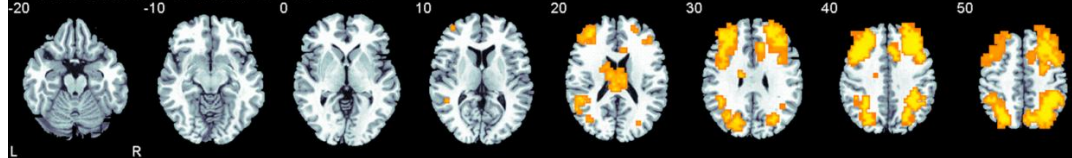


Boys with ADHD under Atomoxetine

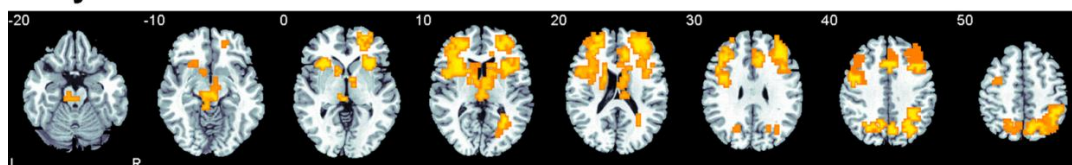


b) 2-Back

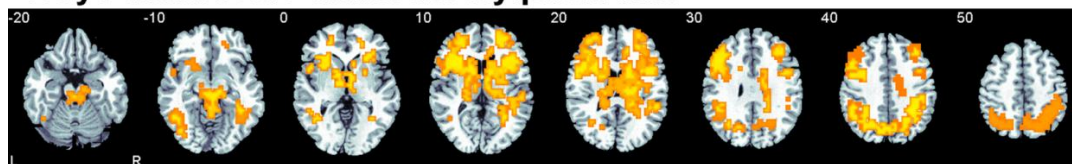
Healthy control boys



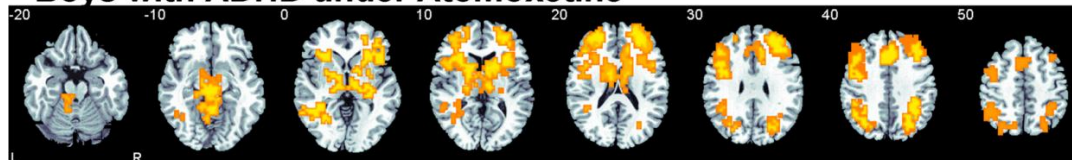
Boys with ADHD under Placebo



Boys with ADHD under Methylphenidate

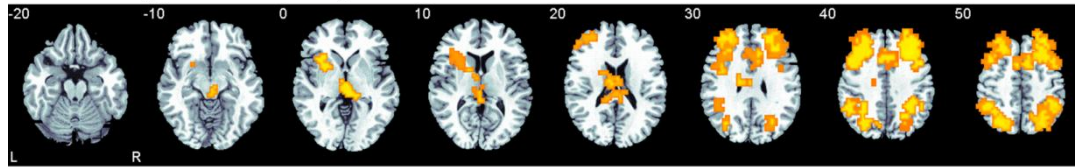


Boys with ADHD under Atomoxetine

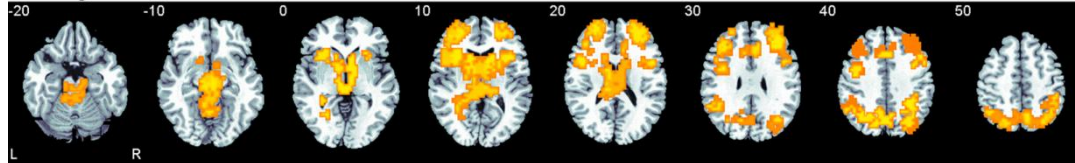


c) 3-Back

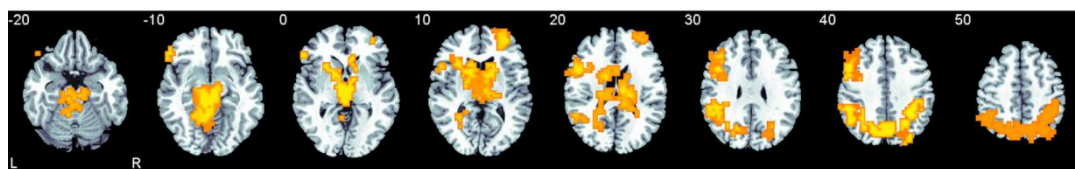
Healthy control boys



Boys with ADHD under Placebo



Boys with ADHD under Methylphenidate



Boys with ADHD under Atomoxetine

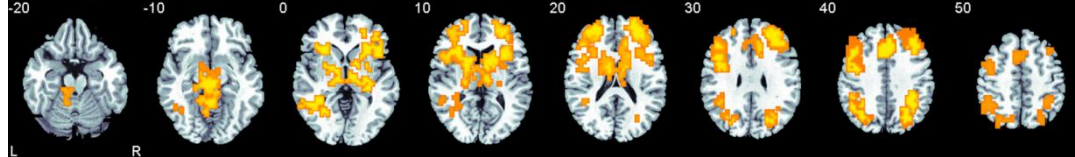


Figure 7.2. Within-group brain activation maps for the two task conditions. Axial sections showing within-group brain activation for the healthy comparison boys and boys with ADHD under each condition (placebo, MPH, ATX) for the contrasts a) 1-Back versus 0-Back, b) 2-Back versus 0-back, c) 3-Back versus 0-Back. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line.

Table 7.3. Brain Activation within each group

Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	P value
a) 1-Back				
Healthy control boys				
R medial/superior frontal gyri	46/9/8	40; 41; 26	98	<0.001
L inferior/medial frontal/premotor gyri	44/8/9/6	-43; 11; 37	47	0.004
R postcentral/inferior parietal gyri	2/40	32; -44; 37	86	<0.001
L inferior/superior parietal gyri	40/7	-29; -48; 37	26	0.009
Boys with ADHD under PLACEBO				
R medial/superior frontal gyri	9/10/46	36; 41; 20	103	<0.001
L medial frontal gyrus	9/46	-25; 33; 20	40	0.002
L inferior frontal/caudate/putamen/pre/postcentral/insula/superior temporal/inferior parietal gyri	44/6/12/3/4/22/40	-43; 11; 4	190	<0.001
R caudate/putamen/premotor/insula/anterior cingulate gyri	6/24/32	11; 22; 26	135	<0.001
R inferior parietal gyrus	40	43; -30; 37	37	0.002
Boys with ADHD under MPH				
L inferior/medial frontal/premotor gyri/insula	44/9/6	-40; 7; 20	45	0.001
L inferior frontal gyrus	44	-58; -15; 4	22	0.005
L inferior parietal gyrus	40	-40; -37; 26	29	0.005
R inferior parietal gyrus/cuneus/precuneus	7/19/40	29; -41; 31	88	<0.001
R medial/inferior temporal gyri	21/37	51; -56; 13	25	0.005

L medial/inferior temporal/medial occipital/fusiform gyri	21/37/18/19	-43; -67; -13	61	0.002
R + L vermis cerebellum/subthalamic nuclei	-	4; -26; -13	76	<0.001
Boys with ADHD under ATX				
R inferior/medial/superior frontal/premotor gyri	44/45/9/10/46/6	29; 33; 26	186	<0.001
L inferior frontal gyri/insula/lenticular nucleus/thalamus	45/47	-29; 30; -2	209	< 0.001
R anterior cingulate/medial frontal/premotor/caudate/putamen/thalamus/insula	24/32/8/6	18; 4; 4	130	<0.001
R putamen/thalamus/insulamedial/superior temporal gyri	21/37/39/22	40; -33; 4	102	<0.001
L medial temporal/fusiform gyri/caudate tail	21/19	-32; -37; -2	53	0.001
R inferior parietal/postcentral gyri	40/1/2/3	32; -44; 31	32	0.001
R + L vermis cerebellum/subthalamic nuclei	-	40; -52; -2	35	0.004
b) 2-Back				
Healthy control boys				
R medial/superior/inferior frontal gyri	10/46/9/8/44	36; 37; 26	287	<0.001
L medial/superior/inferior frontal gyri	10/46/9/8/45	-36; 22; 31	233	<0.001
R anterior cingulate gyrus	24/32	11; 18; 37	37	0.005
R & L thalamus	-	-4; -18; 9	53	0.003
L superior temporal/inferior parietal gyri	22/40	-40; -48; 20	27	0.007
R cuneus/precuneus/middle/superior occipital/inferior parietal gyri	7/18/19/40	29; -63; 42	196	<0.001
L precuneus/occipital/medial temporal/inferior parietal gyri	7/19/39/40	-32; -48; 37	129	<0.001
Boys with ADHD under PLACEBO				
R inferior frontal gyrus/insula/caudate/putamen	44/45/47	29; 26; -2	133	<0.001
R superior/medial frontal gyri	9/10/46	36; 30; 26	187	<0.001
L inferior/middle/superior frontal/pre/postcentral gyri/caudate/putamen/thalamus	44/45/47/46/9/10/6/4	-25; 26; 4	304	<0.001
R + L anterior cingulate gyrus	24/32	11; 37; 9	57	0.002

R subthalamic nuclei/thalamus	-	7; -11; -13	45	0.008
R lingual/middle temporal gyri	18/37	29; -55; 4	26	0.009
R precuneus/inferior/superior parietal gyri	18/19/7/40	11; -59; 37	128	<0.001
L superior occipital gyrus/cuneus	19	-18; -59; 26	33	0.007
Boys with ADHD under MPH				
R + L inferior frontal/middle/precentral gyri/insula/caudate/putamen/thalamus	44/45/47/9/10/46/6	-29; 26; -2	967	<0.001
R middle/superior frontal gyri	46/10/9	40; 41; 26	105	<0.001
R + L anterior cingulate gyrus	32	11; 30; 9	13	0.007
R + L inferior parietal gyrus/precuneus /superior temporal gyri	40/7/19/39	32; -41; 31	257	<0.001
L inferior/medial temporal/medial occipital/fusiform gyri	37/21/19	-36; -52; -13	43	0.005
R superior temporal/ inferior parietal gyri	22/40	51; -37; 9	36	0.006
R fusiform gyrus	19	40; -41; -18	28	0.006
Boys with ADHD under ATX				
R inferior/middle/superior frontal/precentral gyri/insula/caudate/putamen/globus pallidus/thalamus, R + L subthalamic nuclei/L globus pallidus	44/45/47/46/9/10/6	29; 48; 9	926	<0.001
R + L mesial frontal/anterior cingulate/supplementary motor area	8/32/6	-4; 18; 37	79	<0.001
L medial temporal gyri	21/38	-32; -41; -7	48	0.004
R inferior parietal/medial temporal/precuneus	40/39/7/19	32; -48; 31	83	<0.001
L inferior parietal/superior temporal gyri/cuneus/precuneus	40/22/19/7	-32; -48; 31	75	<0.001
c) 3-Back				
Healthy control boys				
L inferior frontal gyrus/putamen	47/45	-25; 26; -7	42	0.006
R superior/middle/inferior frontal gyri	9/46/8/44	32; 30; 31	258	<0.001
L superior/middle/inferior frontal gyri	9/46/8/44	-22; 41; 37	234	<0.001

R + L dorsal anterior cingulate/supplementary motor area	24/32/6	11; 26; 26	82	<0.001
L thalamus/caudate body/mid-cingulate gyrus	23	-7; -7; 9	38	0.007
L thalamus/subthalamic nuclei	-	4; -18; -7	54	0.007
R cuneus/precuneus/superior occipital/inferior/superior parietal gyri	19/7/40	29; -63; 26	133	<0.001
L precuneus/superior occipital/inferior/superior parietal gyri	19/7/40	-22; -63; 42	143	<0.001
Boys with ADHD under PLACEBO				
R + L inferior/middle/superior frontal/precentral gyri/caudate/putamen/thalamus/nucleus accumbens/subthalamic nuclei /hippocampus/parahippocampal/lingual gyri	44/45/47/46/9/10	-22; 59; 9	965	<0.001
L inferior frontal gyrus	44	-36; 4; 26	31	0.005
R + L anterior cingulate gyrus	32	-4; 26; 31	18	0.006
R + L anterior cingulate gyrus	32	7; 26; 20	23	0.007
R + L inferior/superior parietal/superior occipital/precuneus	40/7/18/19	29; -44; 31	268	<0.001
L, cerebellar vermis	-	25; -33; -29	32	0.006
Boys with ADHD under MPH				
R middle/superior frontal gyri	10/46	26; 55; 4	46	<0.001
L inferior frontal gyrus	47	-54; 37; -13	18	0.009
L inferior/middle/superior frontal/precentral/insula/R + L caudate/putamen/globus pallidus/thalamus/subthalamic nuclei/L superior temporal/fusiform gyri	44/45/9/10/6/22/19	-40; 26; 26	624	<0.001
R + L inferior parietal/precuneus/R postcentral gyri	40/7/19/1/2	32; -41; 31	339	<0.001
Boys with ADHD under ATX				
L middle frontal gyrus	10/46	-36; 48; 4	58	0.001
R inferior parietal gyrus/precuneus	40/19/7	36; -48; 31	69	<0.001
L inferior /middle frontal/precentral gyri	44/45/9/6	-36; 22; 26	90	<0.001
R + L inferior frontal/anterior cingulate/supplementary motor/R middle/superior frontal/R + L caudate/putamen/globus pallidus/thalamus/subthalamic nuclei/cerebellum (vermis)	44/45/47/24/32/6/9 /10/46	-25; 26; -2	1134	<0.001

R + L precuneus	7	7:-67; 37	40	0.008
L inferior parietal gyrus	40	-32; -48; 31	83	<0.001

Note: N voxels = number of voxels. L = left; R = right; the maps are thresholded to give less than 1 Type I error 3D cluster per map. Talairach coordinates, number of voxels and areas are included underneath the corresponding cluster.

7.3.2.3. ANOVA between-group comparisons between healthy controls and ADHD boys under placebo, MPH or ATX

Controls compared to patients under placebo

Group effects showed that controls compared to patients under placebo showed enhanced activation in bilateral DLPFC (Table 7.4, Figure 7.3). No areas were enhanced in patients compared to healthy controls. There were no significant WM-load by group interaction effects.

Given that patients had larger error rates than controls in the 2- and 3-Back conditions, we hypothesised that the error rates would be negatively correlated with the DLPFC activation in these conditions. Hence, one-tailed Pearson correlations were conducted in both groups separately between statistical measures of the BOLD response in left and right DLPFC and errors. As expected, activation in right DLPFC was negatively associated with errors within controls during 3-Back ($r=-0.39$, $p<0.04$) and within patients at a trend-level during 2-Back ($r=-0.29$, $p<0.1$). No correlations were observed for left DLPFC activation.

Post-hoc Pearson correlations were conducted within each group separately to examine the linear relationship between IQ scores and BOLD signal response on the clusters of between-group brain activation differences. There were no significant correlations within patients or controls.

Controls compared to patients under MPH

After the single dose of MPH, patients compared to controls showed underactivation in the same left and right DLPFC clusters as under placebo. However, ADHD patients relative to controls showed additional, enhanced activation in a cluster comprising right STG, premotor cortex, striatum, thalamus, insula and reaching into the cerebellar vermis (Table 7.4, Figure 7.3). To test whether the increased right medial fronto-STG-striatal activation in patients under MPH was compensatory for the reduced bilateral DLPFC activation, statistical measures of BOLD response were extracted for each patient in these 3 clusters and correlated with the DLPFC activation clusters as well as with errors. Pearson correlations showed that the medial fronto-STG-striatal activation was negatively correlated with the left DLPFC activation ($r=-0.5$, $p<0.012$) and with errors during the 2-Back condition ($r=-0.52$, $p<0.01$).

A significant interaction of group by WM-load was observed in the left IFC reaching into DLPFC, putamen and anterior insula, due to enhanced activation in patients under MPH relative to controls during 2-Back ($p < 0.01$) (Table 7.4, Figure 7.4). Additional interaction effects were observed in bilateral occipital regions extending to cuneus, due to the enhanced deactivation of this cluster in patients under MPH compared to controls during 2-Back ($p < 0.001$). Within patients, the enhanced deactivation in occipital regions was correlated with reduced errors during 2-Back ($r = -0.47$, $p < 0.019$), and with the abnormally enhanced activation relative to controls in left IFC/DLPFC during 2-Back ($r = -0.5$, $p < 0.012$) and 3-Back ($r = -0.49$, $p < 0.014$).

To test whether the cluster of activation differences in occipital regions and cuneus was due to excessive movement in the ADHD group, Pearson correlations were conducted within patients between movement parameters (mean rotation and translation values) and the SSQs in occipital regions and cuneus under each WM load condition. There were no significant correlations.

Controls compared to patients under ATX

Under the single dose of ATX, patients compared to controls still showed reduced activation in the left DLPFC. However, they no longer showed underactivation of right DLPFC. In addition, abnormally enhanced activation was observed in ADHD relative to controls in a right-lateralised cluster of IFC and STG, reaching deep into insula, thalamus and striatum (Table 7.4, Figure 7.3), which within patients was negatively associated with errors during 2-Back ($r = -0.52$, $p < 0.009$) and at a trend level during 3-Back ($r = -0.35$, $p < 0.066$).

Significant interaction effects of group by WM-load were observed in the ACC and PCC extending to precuneus (Table 7.4, Fig 7.4), due to significantly enhanced activation within patients relative to controls during 1-Back ($p < 0.004$) and enhanced deactivation during 3-Back ($p < 0.005$).

When those subjects whose IQ scores were more than 2 SD above or below average were excluded, findings from all the case-control contrasts remained significant, although at a more lenient p value ($p < 0.03$) (See Appendix Figure A2).

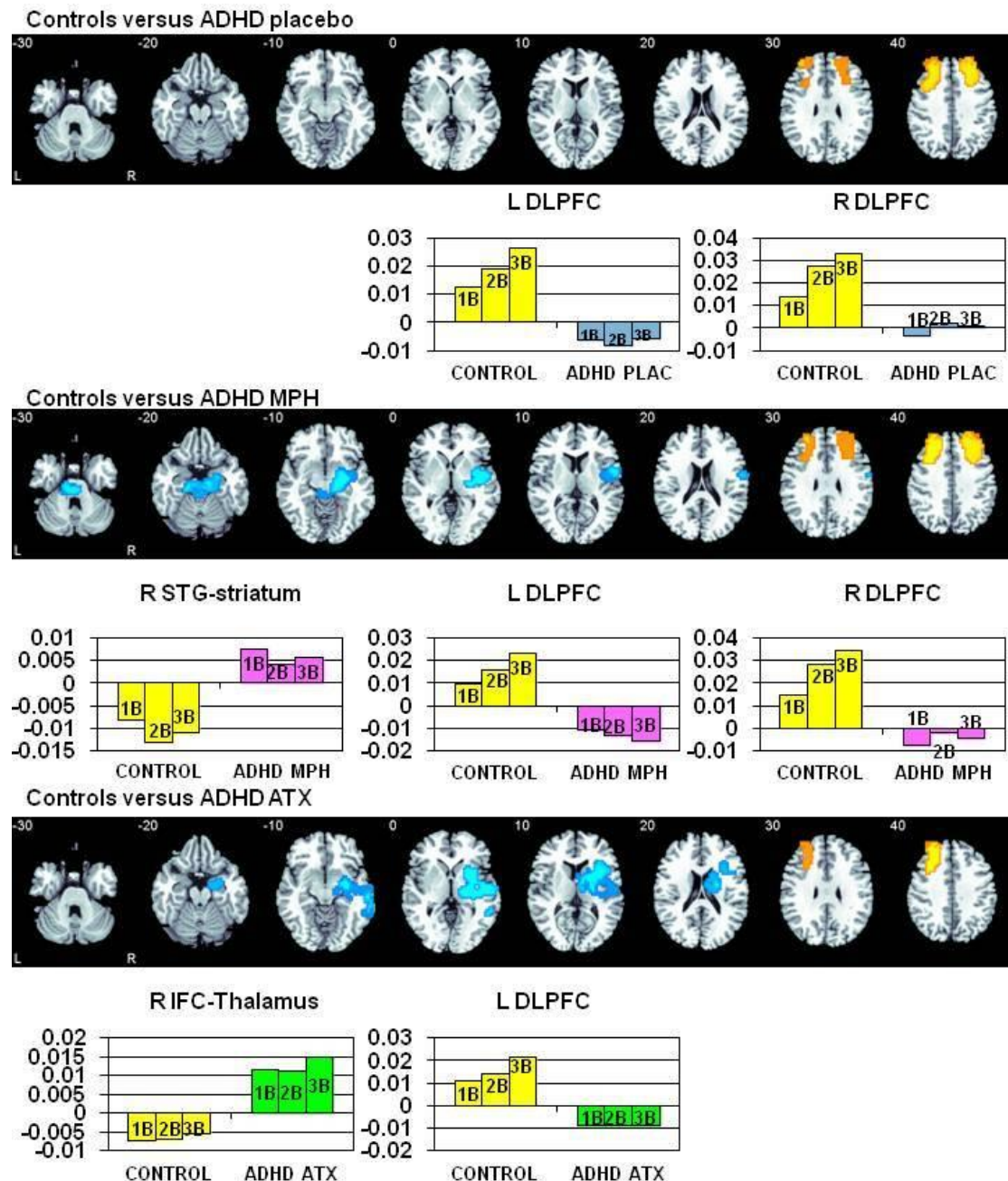


Figure 7.3. Between-group ANOVA comparisons between healthy boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine. Axial sections showing the ANOVA between-group difference effects in brain activation between healthy control boys and boys with ADHD under each condition (placebo, MPH, ATX). Clusters in orange denote areas where control boys showed enhanced activation compared to ADHD boys, clusters in blue denote areas where ADHD boys showed enhanced activation compared to control boys. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain. The maps are thresholded to give less than 1 Type I error 3D cluster per map ($p < 0.01$). The graphs show the BOLD response in each area for each group and WM condition. The x-axis of the graphs corresponds to the statistical measure of the BOLD response in this region. 1B= one-Back, 2B = two-back, 3B = three-back. R = Right, L = Left, DLPFC = dorsolateral prefrontal cortex,

IFC= inferior frontal cortex, PCC= posterior cingulate cortex, BOLD= Blood Oxygen-Level Dependent, Plac= placebo, MPH= Methylphenidate, ATX=Atooxetine.

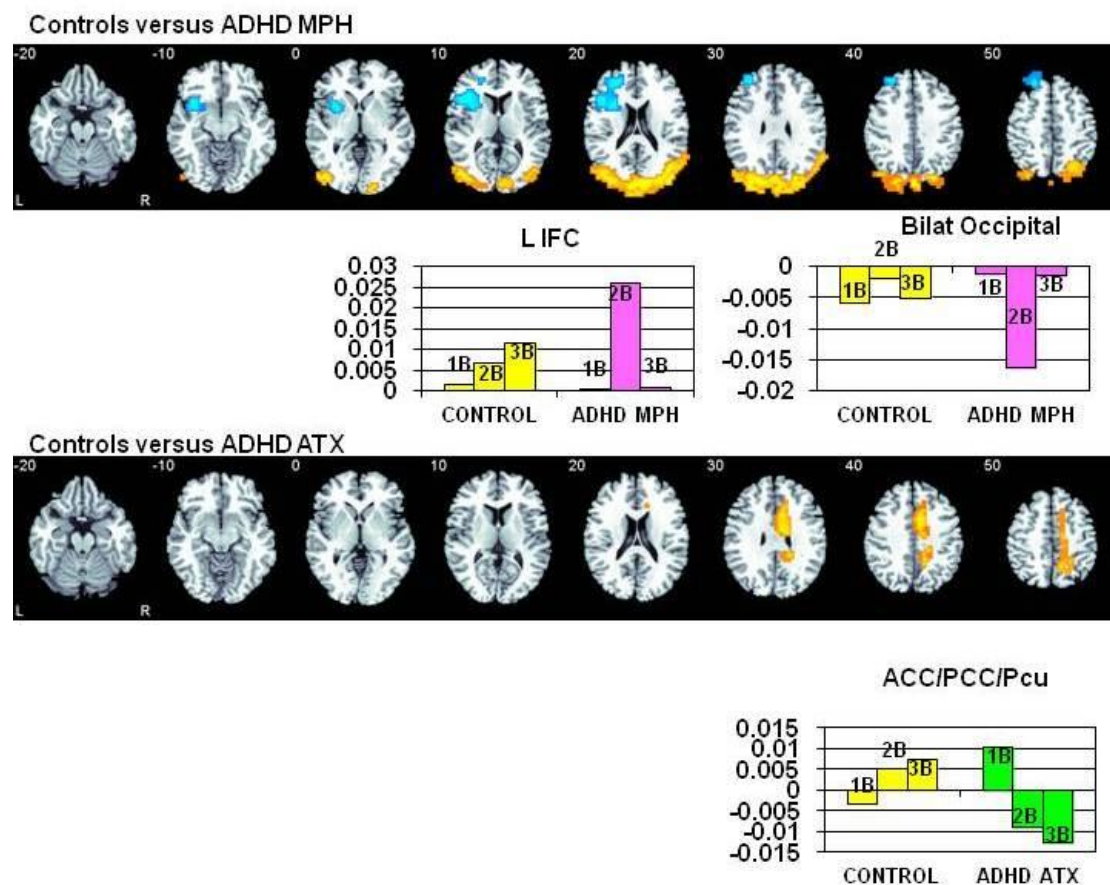


Figure 7.4. Between-group ANOVA interaction effect (Group x WM-load) for the comparison between healthy boys and boys with ADHD under Methylphenidate. Axial sections showing the ANOVA between-group difference effects in brain activation between healthy control boys and boys with ADHD under MPH depending on WM load. Clusters in orange denote areas where control boys showed enhanced activation compared to ADHD boys, clusters in blue denote areas where ADHD boys showed enhanced activation compared to control boys. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain. The graphs show the BOLD response in each area for each group and WM condition . The maps are thresholded to give less than 1 Type I error 3D cluster per map ($p < 0.01$). 1B= one-Back , 2B = two-back, 3B = three-back. R = Right, L = Left, IFC= inferior frontal cortex, ACC/PCC/Pcu= anterior cingulate cortex/posterior cingulate cortex/precuneus. BOLD= Blood Oxygen-Level Dependent, MPH= Methylphenidate.

Table 7.4. Between-group ANOVA differences in brain activation between controls and boys with ADHD under either the Placebo, Methylphenidate or Atomoxetine condition.

Subject Contrast	Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	Cluster P value	Cohen's <i>d</i>
a) Group Effect						
C > ADHD Plac	R medial/superior frontal	9/8	25; 37; 31	129	0.01	1.28
	L medial/superior/inferior frontal	9/8	-25; 44; 31	129	0.008	1.51
C > ADHD MPH	R medial/superior frontal	9/8	25; 44; 31	201	<0.001	1.90
	L medial/superior frontal	9/8	-25; 44; 31	143	0.002	1.73
ADHD MPH > C	R superior temporal/parahippocampal gyri/premotor cortex/basal ganglia/thalamus/ insula/ amygdala/vermis cerebellum	36/22/6	18; -15; -24	297	0.005	1.60
C> ADHD ATX	L medial/superior frontal	9/8	-25; 41; 37	169	0.004	1.65
ADHD ATX >C	R inferior frontal/insula/ medial/superior temporal/insula/amygdala/basal ganglia/thalamus	44/45/21/22	29; -15; -7	395	0.003	1.82
b) Group by WM load Interaction Effect						
C vs ADHD MPH	L inferior/middle/superior frontal/putamen	44/45//10/46/9	-36; 22; 4	237	0.007	0.85
	R + L medial occipital/cuneus/middle temporal gyri	17/18/19/39	-25; -85; 20	546	<0.001	1.18
C vs ADHD ATX	R anterior/posterior cingulate gyri/precuneus	24/32/23/31/7	11;15;26	167	0.004	0.98

Note: N voxels = number of voxels. L = left; R = right; the maps are thresholded to give less than 1 Type I error 3D cluster per map.

7.3.2.4. Significance of the “normalization” effects

We wanted to analyze the significance of the “normalization” effects observed in the between-groups fMRI analysis. Given that the data of the healthy control group was identical across the different case-control comparisons, non-parametric Friedman tests were conducted only within patients to identify whether there were significant differences in brain activation under each drug condition in each of those clusters where the case-control contrasts showed “normalization” effects.

There were significant differences between drug conditions in the right DLPFC (BOLD Placebo: <-0.001 ; BOLD MPH: -0.007 ; BOLD ATX: 0.004 ; χ^2 (2, $N=60$) = 10.43 , $p<0.005$), which, as shown by post-hoc non-parametric Wilcoxon Tests, were due to significant differences between brain activation in patients under MPH relative to that observed when they were under ATX ($p<0.003$) and under placebo ($p<0.018$).

For the cluster of enhanced right fronto-STG-striatum activation under MPH relative to controls, the differences in brain activation within patients under the three drug conditions only reached a trend level (BOLD Placebo: -0.002 ; BOLD MPH: 0.006 ; BOLD ATX: 0.0005 ; χ^2 (2, $N=60$) = 5.63 , $p<0.060$). However, further exploratory post-hoc Wilcoxon tests showed there were significant differences between brain activation when under MPH relative to when under placebo ($p<0.001$) and, at a trend level, also when under MPH relative to ATX ($p<0.095$).

Finally, for the cluster of enhanced right IFC-STG-striato-thalamic activation under ATX relative to controls, there were significant differences between the activation within ADHD boys under the three conditions (median BOLD Placebo: 0.005 ; BOLD MPH: 0.006 ; BOLD ATX: 0.013 ; χ^2 (2, $N=60$) = 9.03 , $p<0.011$). These were due to the differences on brain activation in this clusters when they were under ATX relative to placebo ($p<0.001$) and MPH ($p<0.022$).

7.3.2.5. Significance of the “laterality” effects

In order to test for the significance of the laterality effects on the BOLD signal changes observed in the right DLPFC under MPH and ATX, we conducted a repeated measures analysis within patients with laterality (2 levels: right DLPFC, left DLPFC) and drug condition (3 levels: placebo, MPH and ATX) as within-subjects factors. The

results show a trend for a significant laterality x drug interaction effect ($F(2,118)=2.58$, $p<0.08$), due to the significant differences between ATX and MPH ($p<0.039$), with ATX showing the strongest laterality effects and MPH having no differential laterality effects (Fig 7.5).

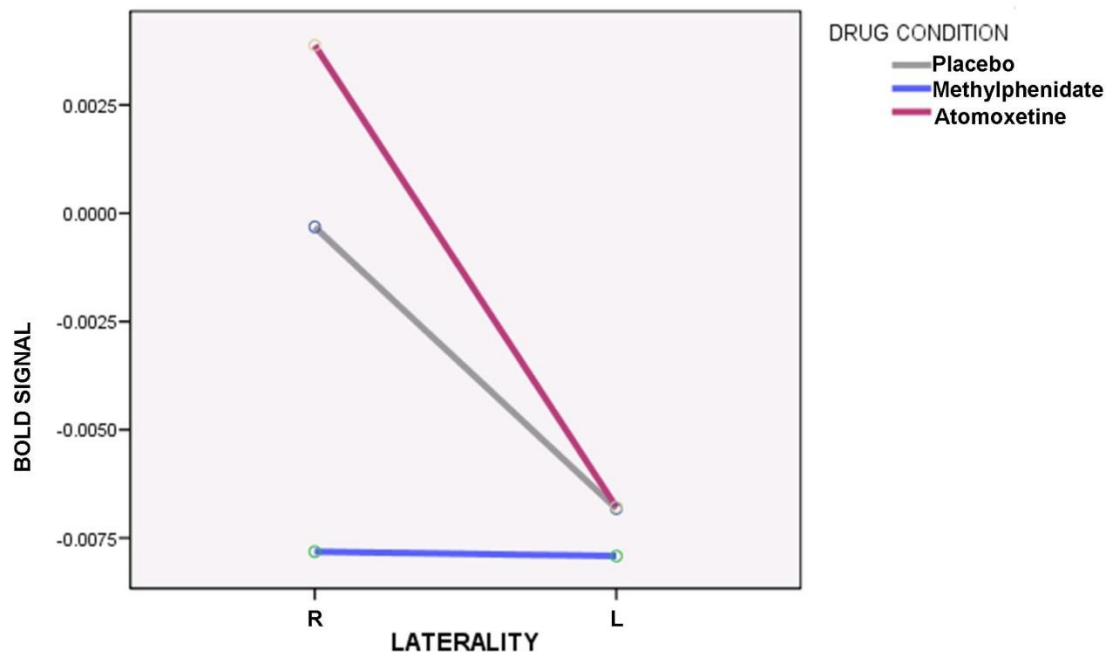


Fig. 7.5. BOLD signal in right and left DLPFC within patients under each drug condition. While MPH had similar effects on BOLD signal in the right and left DLPFC, ATX showed enhanced activation in right DLPFC.

Furthermore, to test whether the interaction group x WM load effects observed when patients were under MPH on the left IFC/DLPFC during the 2-Back condition were specifically left-lateralised, we re-run the between-group comparison analysis at a higher p-value. Only at a $p=0.09$, a small and more dorsally located cluster emerged, in the right medial frontal cortex (27 voxels, peak Talairach coordinates (x;y;z):29; 26; 26; BA 9/46) (Figure 7.6). As can be seen in the figure 7.6, the differences observed in this cluster were due to the progressive increase of activation in this area in healthy controls but not in patients. Therefore, the positive effects of MPH were only observed on left hemispheric prefrontal regions.

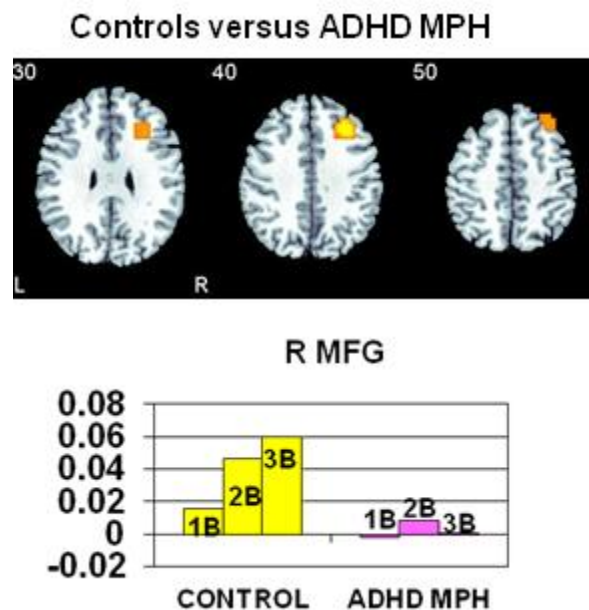


Fig. 7.6. Additional cluster of activation differences in right medial prefrontal cortex observed in the group (healthy controls, boys with ADHD under MPH) x WM load comparison (1-Back, 2-Back, 3-Back) ($p < 0.09$). The graph shows the progressive increase of activation with increasing WM load in the group of healthy control boys, while such increase is not observed in ADHD boys under MPH. 1B= one-back, 2B = two-back, 3B = three-back, R = Right, L= left, MFC= medial frontal cortex, MPH=Methylphenidate

7.3.2.6. ANOVA within-patient comparison between placebo, MPH and ATX

Given the reduced activation in left and right DLPFC, we tested for significant upregulation effects of both drugs in frontal cortex. The Talairach Client (Lancaster et al., 1997; Lancaster et al., 2000) was used to define an anatomical mask of the frontal lobe, restricting the analysis to those voxels present in the mask. A significant effect of drug condition was observed in a cluster in the right DLPFC (13 voxels, peak Talairach coordinates (x;y;z):25; 44; 26; BA 10/9 $p < 0.044$), which was due to significantly enhanced activation when under ATX relative to MPH ($p < 0.002$), as well as when under placebo relative to MPH ($p < 0.01$) (Figure 7.7a). Activation in this cluster was negatively correlated with errors during 2-Back under ATX ($r = -0.53$, $p < 0.008$), during 3-Back under placebo ($r = -0.40$, $p < 0.04$) and during 1-Back under MPH ($r = -0.48$, $p < 0.015$).

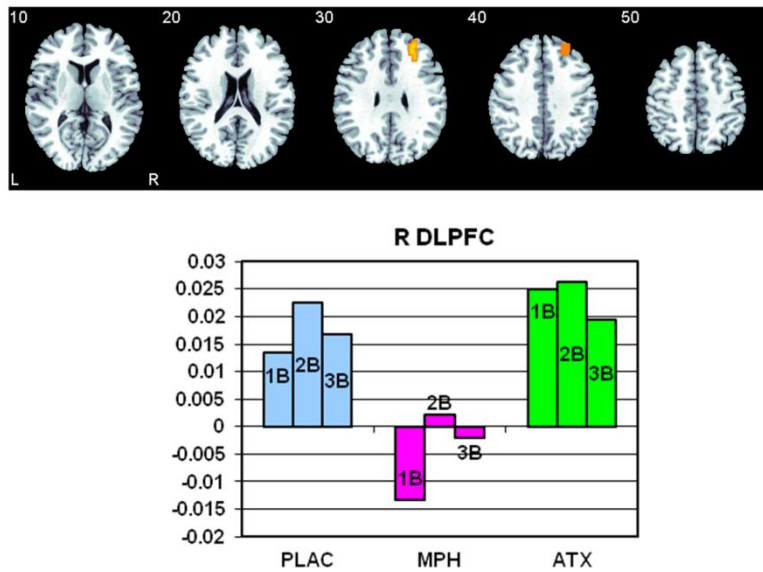
The same analysis was conducted at a higher p-value, in order to investigate whether the effects of ATX were bilateral or exclusively right-lateralised. At $p < 0.07$, a small cluster of activation difference was observed in the left premotor cortex (4

voxels, peak Talairach coordinates (x;y;z): -51;-11;26; BA6). However, as can be seen in Fig 7.8a, in this case was due to the effects of MPH relative to Placebo ($p<0.001$) and MPH relative to ATX ($P<0.001$).

Significant interaction effects of drug condition by WM-load were observed in one cluster comprising left IFC (14 voxels, peak Talairach coordinates (x;y;z):-36; 22; 9; BA 44/45; $p<0.019$) (Figure 7.7b), due to significantly enhanced activation in this cluster during 2-Back when under MPH compared to placebo ($p<0.001$) and ATX ($p<0.015$). There were no significant correlations between activation in this cluster and performance. The same interaction analysis was conducted at a higher p-value, in order to investigate whether the effects of MPH were bilateral or exclusively left-lateralised. At $p<0.05$, a small cluster of brain activation difference was observed in the more ventral location of right OFC extending to putamen (7 voxels, peak Talairach coordinates (x;y;z):22; 11; -18; BA 47). However, and as can be seen in Fig 7.8b, in this case it was due to the significant differences between the effects of placebo and ATX during 2-back ($p<0.03$).

Repeated measures ANOVAs showed no practice effects on the extracted BOLD response measures.

a) Effect of drug condition



b) Interaction effects drug condition x WM load

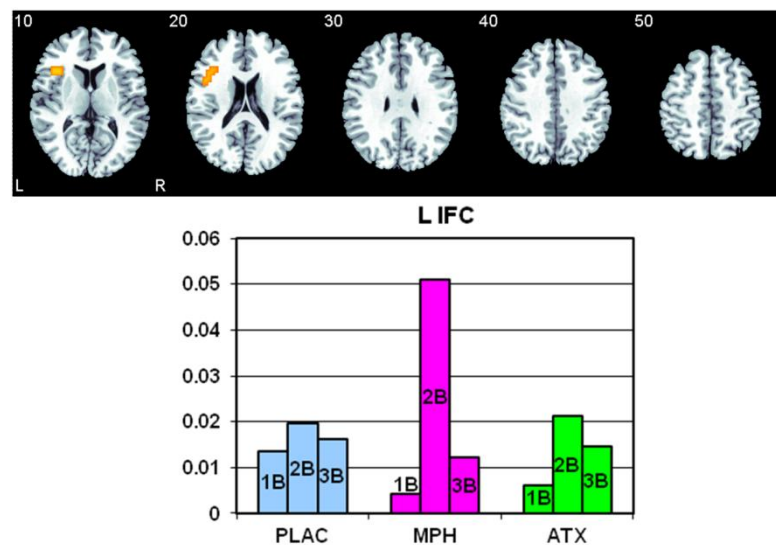
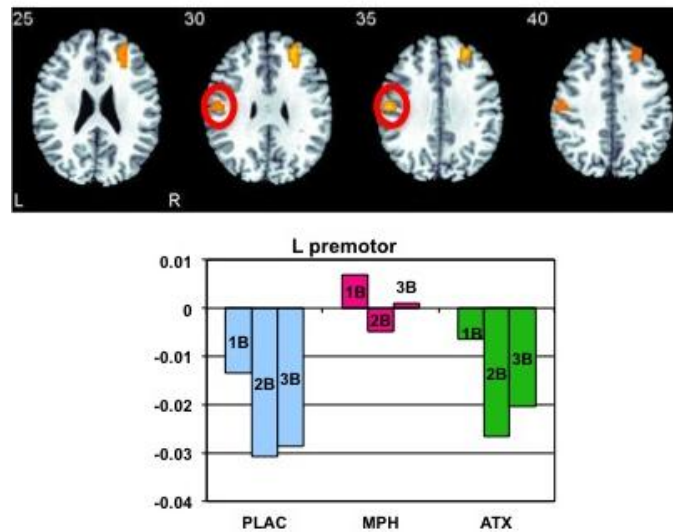


Figure 7.7. Results of the repeated measures ANOVA analyses within ADHD boys, showing the effects for a) drug condition and b) interaction drug condition by WM-load interaction effects within ADHD boys. Axial sections showing the repeated measures ANOVA results for a) drug condition and b) drug condition by WM-load interaction effects within ADHD patients (placebo, MPH, ATX). Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain. The maps are thresholded to give less than 1 Type I error 3D cluster per map ($p < 0.01$). The graphs show the BOLD response in each area for each medication and WM condition. 1B= one-back, 2B= two-back, 3B= three-back, R = Right, L= left, DLPFC= dorsolateral prefrontal cortex, IFC= inferior frontal cortex, BOLD= Blood Oxygen-Level Dependent, MPH= Methylphenidate, ATX=Atomoxetine.

**a) Effect of drug condition:
additional cluster at $p=0.07$**



**b) Interaction effects drug condition x
WM load: additional cluster at $p=0.05$**

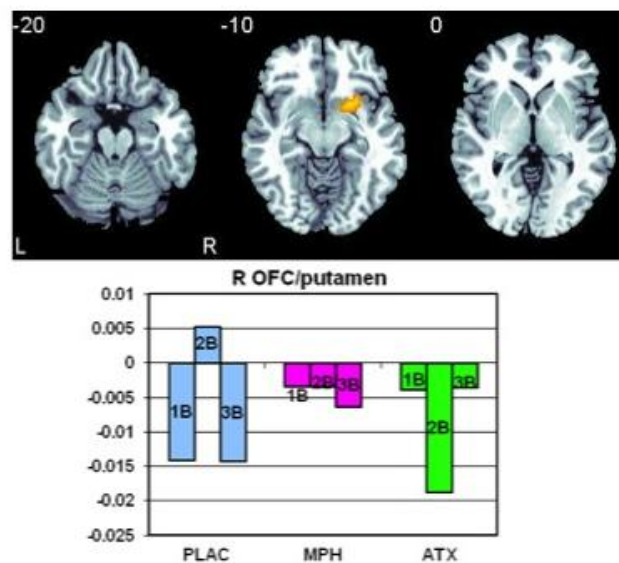


Figure 7.8. Additional cluster of activation differences when repeated measures ANOVA analyses within ADHD boys were conducted at higher p values, showing the effects for a) drug condition and b) interaction drug condition by WM-load interaction effects within ADHD boys. Axial sections showing the repeated measures ANOVA results for a) drug condition ($p<0.07$) and b) drug condition by WM-load interaction effects within ADHD patients (placebo, MPH, ATX) ($p<0.05$). The graph shows the BOLD response in this cluster for each medication and WM condition. 1B= one-back, 2B = two-back, 3B = three-back, R = Right, L= left, OFC= orbitofrontal cortex, Plac=Placebo, MPH=

Methylphenidate, ATX=Atomoxetine. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

7.4. Discussion

To our knowledge, this is the first fMRI comparison between single dose challenges of MPH and ATX on brain activation in medication-naïve children with ADHD. We show both shared and drug-specific effects of both drugs on neural correlates of WM. Medication-naïve ADHD boys under placebo relative to controls showed impaired performance under high but not low WM-load and underactivated left and right DLPFC, which was normalised by both drugs. ATX had drug-specific effects on right DLPFC: within patients, ATX significantly upregulated right DLPFC activation relative to MPH. Furthermore, relative to MPH, ATX had a drug-specific significant normalisation effects on this region, which was underactivated relative to controls under placebo and MPH. By contrast, MPH showed a drug-specific WM load-dependent effect on left-lateralised IFC, which was upregulated during 2-Back both relative to controls as well as relative to ATX and placebo in the within-subject contrast. Both drugs shared WM load-dependent deactivation effects on midline ACC-PCC areas for ATX, and in bilateral occipital regions for MPH, which were negatively associated with improved performance, potentially due to the deactivation of regions of the DMN. Both drugs, in addition, elicited abnormally enhanced activation in patients relative to controls in different fronto-STG-striatal networks, which were associated with improved performance, suggesting a compensatory effect.

Thus, the findings show both shared effects as well as drug-specific laterality effects in prefrontal WM regions. ATX had a drug-specific normalisation and upregulation effect on right-hemispheric DLPFC relative to MPH across all WM load conditions. MPH, by contrast, upregulated and enhanced left IFC, but only during the 2-Back condition, relative to ATX and placebo within patients and relative to controls in the case-control comparison. Both drugs had shared effects of increasing fronto-STG-striatal activation relative to controls, while also eliciting DMN deactivation during higher WM load conditions, both of which improved WM performance in patients.

ADHD patients under placebo showed no deficits during the relatively easy WM task condition, but made significantly more errors than controls during the 2-Back and 3-Back conditions. The findings show WM load-dependent impaired

performance relative to controls and are in line with previous evidence for deficits on complex executive function paradigms in ADHD patients but not in simpler cognitive tasks (Willcutt et al., 2005), in line with previous evidence for WM deficits (Martinussen et al., 2005). Both drugs showed a beneficial effect on these performance deficits, since they were normalised under both drug conditions.

Compared to controls, patients showed underactivation in bilateral DLPFC, a key region for WM, involved in the storage and coding of the temporal sequence of stimuli (Owen et al., 2005). The findings extend previous findings of underfunctioning of DLPFC in adult ADHD during WM (Valera et al., 2010) and in ADHD children during other cognitive control tasks (Christakou et al., 2012; Cubillo et al., 2012; Rubia, 2011).

The most interesting findings are those of drug-specific lateralisation effects on frontal activations during task performance. ATX relative to MPH showed a drug-specific right-hemispheric frontal upregulation and normalisation effect in right DLPFC. MPH showed a drug-specific left-lateralised WM-load dependent effect on left IFC/DLPFC activation during the 2-Back condition, which was upregulated within patients relative to ATX and placebo and abnormally enhanced in patients relative to controls. WM is mediated in the DLPFC by noradrenergic $\alpha 2$ receptors that increase neural “signal” (increased firing to relevant stimuli) and by dopaminergic D1 receptors that decrease “noise” (suppressing firing to irrelevant stimuli) (Gamo et al., 2010). Although ATX affects both DA and NE in the PFC (Bymaster et al., 2002), in non-human primates it increases “signal” more frequently than it decreased “noise” (Gamo et al., 2010), suggesting relatively stronger effects on NE-mediated WM networks. Furthermore, the shared enhanced, presumably compensatory activation in fronto-STG-striatal regions reached the right IFC only when patients were under ATX. The right IFC in particular has been associated with WM load processing (Baier et al., 2010). These right-lateralised drug-specific upregulation and normalisation effects of ATX on right-hemispheric frontal regions potentially suggest a stronger noradrenergic implication in mediating right frontal activation during WM (Gamo et al., 2010), in line with the notion of a stronger right-hemispheric lateralisation of noradrenergically modulated networks (Tucker & Williamson, 1984). This study shows for the first time that upregulation of right frontolateral activation is not only observed with a single dose of ATX in healthy adults (Chamberlain et al., 2009; Graf et al., 2011), but also in children with ADHD, implying similar mechanisms of action

in both healthy subjects and ADHD patients. Furthermore, and most importantly, we show that, during WM, the right frontal normalisation and upregulation effects with ATX were drug-specific relative to MPH.

The results are suggestive of potentially stronger right-hemispheric frontal upregulation and normalisation effects of ATX relative to MPH during WM, and of drug-specific left-lateralised WM load-dependent effects of MPH relative to ATX and placebo. The findings would be in line with previous evidence for increased levels of DA within left-lateralised sub-cortical structures (Flor-Henry, 1986) and more strongly left-lateralised DA system (Glick, Ross, & Hough, 1982). The left IFC is important for subvocal rehearsal processes during WM (Owen et al., 2005; Smith, Jonides, Marshuetz, & Koeppe, 1998), is also an important area for cognitive control (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011) and mediates selective attention and performance monitoring (Derrfuss et al., 2005; Stevens et al., 2009), necessary to correctly perform the task. Furthermore, during WM maintenance, enhanced dopaminergic function in the caudate has been associated with increased left IFC activation (Landau, Lal, O'Neil, Baker, & Jagust, 2009), and therefore the findings may possibly reflect that association between dopaminergic function in the striatum and left IFC activation during WM. However, future studies should further examine the drug-specific laterality of these effects. These results extend previous findings of fronto-striatal upregulation and/or normalisation in ADHD children with a single dose of MPH during WM (Prehn-Kristensen et al., 2011), performance monitoring (Rubia, Halari, Mohammad, et al., 2011), TD (Rubia, Halari, Christakou, et al., 2009), and inhibition (Epstein et al., 2007; Vaidya et al., 1998), some of which were also, like here, predominantly left-hemispheric (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009).

Both MPH and ATX elicited enhanced deactivation in regions of the DMN in ADHD relative to controls during the high WM load conditions, suggesting that catecholamine agonists work not only by increasing task-positive but also by switching off task-negative DMN activation. ATX showed progressively stronger deactivation in ACC-PCC with increasing WM load. MPH, on the other hand, showed enhanced deactivation in bilateral occipital regions during 2-Back, associated with improved performance. The DMN is associated with stimulus-independent thought and self-referential mental activity and is typically anti-correlated with networks

engaged by effortful cognitive tasks (Broyd et al., 2009). Problems with deactivation of the DMN have been linked to attention lapses in ADHD (Broyd et al., 2009; Fassbender et al., 2009; Sonuga-Barke & Castellanos, 2007). In children with ADHD, a single dose of MPH has previously been shown to enhance DMN deactivation during a GNG task (Liddle et al., 2010). We thus extend these findings to another task and show for the first time that not only MPH but also ATX enhances task-related DMN deactivation in ADHD children. The findings also extend previous findings of enhanced DMN deactivation after single doses of MPH and ATX in healthy adults during WM (Marquand et al., 2011) to a patient group with ADHD. The negative correlation within patients between the more deactivated bilateral occipital regions under MPH and the abnormally enhanced task-positive left IFC/DLPFC activation relative to controls, as well as the correlation with less errors, may reflect a strengthening of attention networks, which are typically enhanced with reduced DMN activity (Fox et al., 2005).

An alternative explanation for the reduced activation in occipital regions when patients were under MPH is also possible. Occipital cortex, cuneus, precuneus and posterior cingulate cortex have consistently been involved in visuo-spatial attention processes (Ardekani et al., 2002; Kiehl et al., 2001; Madden, Whiting, Provenza, & Huettel, 2004; Mesulam et al., 2001; Small et al., 2003). Cholinergic systems have been shown to affect not only sensory processing but also WM processes, increasing the efficiency of visual processing regions and reducing the necessary executive prefrontal processing typically involved in WM (Bentley, Driver, & Dolan, 2011; Furey, Pietrini, & Haxby, 2000). MPH may therefore have affected positively the imbalance between dopaminergic and anticholinergic systems, necessary for adequate cognitive function (Levin, McGurk, Rose, & Butcher, 1990). The increased function in DA-regulated WM networks involving the IFC/DLPFC may have downregulated cholinergic function in occipital regions, hence the reduced activation in these areas. It may be thus hypothesized that MPH may have reduced the activation observed in occipital areas during 2-Back as a consequence of the reduced need for bottom-up visuo-spatial processing, given the increased involvement of the top-down left IFC/DLPFC activation, which would be further supported by the negative correlation between the activation in these two clusters. However, reduction with MPH on occipital areas of visuo-spatial attention is not in line with evidence for reduced activation in such regions in children with ADHD (Booth et al., 2005; Hart, Radua,

Nakao, et al., 2012; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011; Vance et al., 2007) and evidence that MPH has been shown to increase and even normalise reduced occipital activation within children with ADHD relative to healthy control boys during motor response inhibition (Rubia, Halari, Mohammad, et al., 2011).

Another alternative hypothesis could be that activation differences in occipital cortex may suggest potential movement issues. However, there was no significant association between movement parameters and brain activation within patients. Thus, it is unlikely that occipital differences on brain activation were due to movement artefacts. Therefore, further studies are needed to identify the potential mechanisms by which MPH administration reduces activation in occipital, cuneus and PCC regions.

Both drugs showed abnormally enhanced fronto-STG-striatal activation in ADHD boys relative to controls, although in somewhat different locations, affecting premotor cortex with MPH and right IFC with ATX. The findings echo previous findings of fronto-striatal upregulation/normalisation in ADHD children with MPH during WM (Prehn-Kristensen et al., 2011) and other cognitive control tasks (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998). The findings also extend for the first time previous evidence of enhanced IFC/STG activation after a single dose ATX challenge in healthy adults (Chamberlain et al., 2009) to a pediatric ADHD sample. Furthermore, the upregulation effect of MPH of STG parallels previous findings of STG upregulation/normalisation effects in medication-naïve children with ADHD during other executive function tasks (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009). We hypothesise that the upregulation effects of ATX on right fronto-STG-striatal networks known to mediate WM (Owen et al., 2005; Wang, 2001) may have been due to direct effects on frontal and thalamic activation, which may indirectly have enhanced striatal activation (Easton, Marshall, Fone, & Marsden, 2007; Nijima et al., 2010).

The strength of the study is the double-blind, placebo-controlled design and the recruitment of medication-naïve children with ADHD, thus avoiding the potential confound of a previous history of stimulant medication (Frodl & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011). A limitation of the study is that due to ethical, feasibility and financial reasons, healthy controls performed the task only once, unmedicated. However, the counterbalanced randomized design for the ADHD

group adequately controlled for practice effects in patients. Furthermore, we found no order effects on performance or brain activation within patients. Therefore, although we could not directly measure the practice effects in the between group analyses, we assume that they were unlikely to have contributed to performance or brain activation differences between patients and controls. However, it needs to be highlighted that such assumption must be made with caution. We could only test for the presence of potential order effects within subjects, conducted in a very small sample. Therefore, the power to detect potential order effects is severely reduced. Furthermore, given the reduced number of participants on each condition, it was not possible to test for potential sequence effects derived from the randomisation order. Thus, the administration of the drug conditions in a determined randomization order may have enhanced or reduced their effects. Further studies with sufficiently large samples should be conducted to rule out this possibility. In addition, the wider age range in the age of the healthy control group relative to the ADHD boys may have affected the results by widening the between-groups differences in a disorder that has shown to be associated with neurodevelopmental delay (Rubia, 2007; Shaw et al., 2007; Shaw et al., 2012). Therefore, future studies should ideally compare more closely age-matched groups.

An important caveat is that while MPH has an immediate effect on ADHD symptoms (Greenhill et al., 2001), ATX reaches its maximum clinical efficacy after 12 weeks of treatment (Montoya et al., 2009). This investigation of acute mechanisms of action is a first step towards improving our understanding of drug-specific effects on brain activation and cognition, avoiding potential confounds of long-term treatment such as symptomatic improvement, side effects or chronic effects on brain activation. Given the differences of the two drugs in temporal courses to clinical efficacy, however, future studies should also compare their long-term effects on brain activation when they have reached maximum clinical efficacy.

In conclusion, the findings show both drug-specific as well as shared effects on task-positive and task-negative WM networks. ATX appears to be more potent than MPH in upregulating and normalising WM-related right DLPFC dysfunction in ADHD, while MPH appears to upregulate compensatory activation of left IFC activation, but only during the 2-Back condition.

CHAPTER 8: DIFFERENTIAL NEUROFUNCTIONAL EFFECTS OF METHYLPHENIDATE AND ATOMOXETINE IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER DURING TIME PERCEPTION¹

8.1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is defined by problems with inattention, impulsivity and hyperactivity (DSM-IV-TR)(American Psychiatric Association, 2000). Children with ADHD are impaired in EF (Willcutt et al., 2005) but also in temporal processes (Rubia, Halari, Christakou, et al., 2009), particularly TD (Rubia, Smith, et al., 2007a; Smith et al., 2002) which has been shown to be one of the best discriminatory measures for ADHD among a large battery of tasks (Rubia, Smith, et al., 2007a). Using fMRI, TD deficits have been shown to be underpinned by neurofunctional deficits in fronto-striatal regions, including right IFC and DLPFC, SMA, ACC, the basal ganglia and cerebellum (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008).

One of the most frequently prescribed medications for ADHD is the stimulant MPH, which blocks DAT in the striatum (Volkow, Wang, Fowler, Gatley, et al., 1998) and NET in NET-rich cortical regions, including PFC, where it increases concentrations of both DA and NE (Hannestad et al., 2010). There is a strong association between DA, the striatum and fine temporal processes (Takahashi, 2007) and accordingly, the striatal DA agonist MPH has been shown to improve motor timing deficits in children with ADHD in the millisecond (Ben-Pazi et al., 2006; Rubia et al, 2003) and second range (Baldwin et al, 2004; Ben-Pazi et al., 2006). FMRI studies have shown that MPH consistently upregulates and normalises fronto-striatal activation during EF (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Shafritz et al., 2004). The only fMRI study investigating the influence of MPH on brain function in patients with ADHD during TD showed that MPH significantly enhanced left inferior and right DLPFC, ACC and cerebellum and completely normalised these fronto-striato-cerebellar differences between controls and patients on placebo (Rubia, Halari, Christakou, et al., 2009).

Another frequently prescribed medication for patients with ADHD is the non-stimulant ATX. Two meta-analyses have shown that ATX demonstrates comparable

¹ This chapter has been submitted as a paper to Biological Psychiatry, where is under re-revision

efficacy rates with MPH in reducing ADHD symptoms (Hanwella et al., 2011; Hazell et al., 2010) and, as a non-stimulant, has less potential for abuse but takes longer to have a clinical effect on behaviour (Hazell et al., 2010). ATX is a selective presynaptic blocker of NETs (Bymaster et al., 2002), leading to enhanced NE and DA in PFC but also significant effects in other regions including ACC, thalamus, locus coeruleus and cerebellum (Takano et al., 2009). Importantly, compared with MPH, ATX has no direct effect on the basal ganglia (Takano et al., 2009).

In healthy adults, a single dose of ATX increased right IFC and STG activation during cognitive control (Chamberlain et al., 2009; Graf et al., 2011). Multivariate pattern recognition analyses comparing single doses of MPH and ATX during WM in healthy adults showed a stronger effect of MPH on upregulating task relevant networks, but a relatively stronger effect of ATX on the suppression of the DMN (Marquand et al., 2011). Nevertheless, no study has carried out a single dose challenge, investigating the immediate effects of ATX on brain function in ADHD or compared its effects on brain activation in ADHD to those of MPH. We focused on TD since it is a disorder-sensitive function (Rubia, Smith, et al., 2007a; Smith et al., 2008; Smith et al., 2002) shown to be mediated by fronto-striatal networks (Rubia, 2006) (Wiener et al., 2010) and modified by dopamine agonists (Baldwin et al., 2004; Rubia, Noorloos, et al., 2003).

Given the strong association between DA and fronto-striatal networks in TD (Rubia, 2006) and the evidence for positive effects of MPH on time estimation (Baldwin et al., 2004; Rubia, Noorloos, et al., 2003) and its underlying fronto-striatal networks in ADHD (Rubia, Halari, Christakou, et al., 2009) we hypothesised that MPH would enhance TD performance and its associated fronto-striatal correlates. However, we proposed that ATX would also increase right fronto-cortical activation, as observed in healthy adults during tasks of cognitive control (Chamberlain et al., 2009; Graf et al., 2011).

8.2. Methods and Materials

8.2.1. Participants

Twenty nine medication-naïve right-handed adolescent boys between 10-17 years with a clinical diagnosis of inattentive/ hyperactive-impulsive combined ADHD as assessed by an experienced child psychiatrist using the standardized Maudsley

diagnostic interview (Goldberg & Murray, 2002) which assesses ADHD according to DSM-IV-TR criteria (American Psychiatric Association, 2000) were recruited from clinics. A multidisciplinary clinical team participated in the assessment, which included information from semi-structured clinical assessment interviews with parents/carers, questionnaires from parents and teachers, school reports, developmental history, cognitive assessments and behavioural observation of the child. The presence of learning disability was concluded from the information provided by parents and school during the clinical and cognitive assessments, or by the presence of significant discrepancies between verbal and performance IQ subscores, which is considered as an indicator of potential learning difficulties.

Nine patients were excluded due to: neurological abnormalities detected during the scan (N=1), technical difficulties that led to loss of data (N=2), braces (N=1), IQ<70 (N=1) or intolerance to the scanning situation (N=4). In line with their diagnoses, all patients scored above clinical cut-off for hyperactive/ inattentive symptoms on the parental SDQ (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000), and the CPRS-R (Conners et al., 1998), and below clinical cut-off on the SCQ (Rutter et al., 2003). They were scanned over three consecutive weeks using a double-blind, pseudo-randomised, cross-over drug design, receiving a single dose of either placebo (Vitamin C, 50mg), MPH (Equasym 0.3mg/kg: range 5–20mg) or ATX (Strattera 1mg/kg: range 16-66 mg), all identical in appearance. Dosages were determined following NICE guidelines at the time of the study for typical clinical efficacious dosages with minimal side effects (National Institute for Health and Clinical Excellence, 2008). As suggested by evidence from pharmacokinetics studies, both medications were administered 1.5 hours before the scan to allow for maximum absorption (Chan et al., 1983; Swanson & Volkow, 2002; Witcher et al., 2003).

Twenty-one male right-handed healthy boys between 10-17 years old were recruited through advertisements. They scored below clinical cut-off for the SDQ, SCQ, and CPRS. One healthy boy was excluded due to CPRS-R and SDQ scores above clinical threshold. Controls were scanned once, unmedicated, for feasibility and ethical reasons. The final subject numbers were therefore 20 ADHD and 20 controls (Table 8.1).

Participants were excluded if they had learning disability, reading, speech or language disorder, neurological abnormalities, epilepsy, drugs or substance abuse or any comorbid psychiatric disorders (except for conduct disorder and oppositional

defiant disorder in the ADHD group: $N=2$). When parental reports for potential participants were suggestive of the presence of such difficulties, questions addressing each of the criteria for ODD/CD were included in the semi-structured interviews. Thus, despite the fact that the mean score in the ADHD group for oppositional problems in the CPRS-R and behavioural difficulties in the SDQ scales were above clinical cut-offs (Table 8.1), only two cases received the formal diagnosis of ODD/CD.

One-way ANOVA showed no group differences for age ($F(1,38)=2$, $p<0.15$). All participants had an $IQ>70$ on the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) but significant group differences were observed (mean controls: 113 (10) mean ADHD: 91 (11): $F(1,38)=41$, $p<0.0001$).

IQ scores have consistently been shown to be lower in patients with ADHD than in age-matched healthy controls (Bridgett & Walker, 2006; Kuntsi et al., 2004). It has furthermore been shown that measures of perceptual timing vary with IQ scores (Paule et al., 1999; Wearden et al., 1997), suggesting that abnormal timing functions in ADHD might be associated with low IQ. Indeed, such a link has been demonstrated in children with ADHD during time perception and temporal foresight tasks, including duration reproduction (Smith et al., 2002; Toplak et al., 2003), estimation (Barkley et al., 2001), and temporal discounting tasks (Bitsakou et al., 2009; Kuntsi et al., 2001; Marco et al., 2009). Overall, IQ seems to mediate specific abnormalities of timing functions, in particular reproduction of temporal intervals, but this is not consistently observed.

We conducted an exploratory analysis comparing brain activation between healthy controls and children with ADHD under placebo with and without using IQ as a covariate. When using IQ as a covariate, the resulting clusters of activation differences between groups included only those that have been closely related with time perception. These included the IFC/DLPFC and the SMA/ACC, both of which which have been associated with the estimation and discrimination of stimulus durations in the seconds and milliseconds' range (Coull & Nobre, 2008; Lewis & Miall, 2006b; Rubia, 2006; Rubia & Smith, 2004; Shih et al., 2009; Smith et al., 2003; Wiener et al., 2010). On the other hand, when IQ scores were not used as a covariate, the areas included the above mentioned plus two additional clusters of activation differences in bilateral parietal regions. These are not areas typically involved in time perception processes per se, but rather their role is more indirectly associated to time

processes by facilitating sustained attention to time (Rubia, 2006). Thus, as the results were restricted to areas directly associated to time perception processes when IQ was used as a covariate, this option was selected for the case-control fMRI and performance analyses.

Participants were paid £50 for each visit. Written informed consent and assent were obtained and the study was approved by the local ethics committee.

Table 8.1. Sample characteristics for healthy control boys and patients with ADHD.

Variables	Controls (20) Mean (SD)	ADHD (20) Mean (SD)
Age (years, months)	13y, 11m (2y, 4m)	12y, 11m (1y, 8m)
Age range (years, months)	10y, 8m - 17y,6m	10y, 1m – 15y, 6m
IQ	113 (10)	91 (11)
SDQ Hyperactive-impulsive/ Inattentive Subscale	2 (2)	8 (2)
SDQ – Total score	4 (4)	22 (7)
SDQ Emotional difficulties subscale	1 (2)	4 (3)
SDQ Behavioural difficulties subscale	0 (1)	6 (3)
SDQ Getting along difficulties subscale	1 (1)	3 (3)
SDQ Kind and helpful behaviours subscale	9 (2)	5 (2)
SCQ Total	1 (1)	9 (5)
CPRS-R Total T score	44 (5)	78 (11)
CPRS-R oppositional T score	43 (4)	76 (13)
CPRS-R Cognitive/ inattention problems T Score	45 (4)	69 (9)
CPRS-R hyperactivity T score	47 (4)	79 (14)
CPRS-R anxious/shy T score	49 (10)	60 (16)
CPRS-R Perfectionism T score	44 (4)	59 (16)
CPRS-R social problems T score	47 (3)	61 (15)
CPRS-R Psychosomatic T score	49 (7)	63 (16)
CPRS-R Global Index: restless impulsive T score	44 (3)	76 (12)
CPRS-R Global Index: emotional liability T score	45 (5)	72 (15)
CPRS-R ADHD T score	44 (4)	75 (8)

Note: SDQ=Strengths and Difficulties Questionnaire; CPRS-R: Conners' Parent Rating Scale; SD= Standard Deviation

8.2.2. Time Discrimination Task

After one practice session outside the scanner, the task was visually presented in the MRI scanner via a prism from a liquid crystal diode projector. The 5 min block-design task consisted of 5 x 30-second alternated blocks for two conditions: TD (active condition) and temporal order judgement (TOJ) (control condition), which was always presented first. The TD condition began with the appearance of a centrally located grey circle (5 cm in diameter) with the letter “L” for 3 seconds. This was followed by two equally sized red (left side of screen) and green circles (right side of screen), appearing consecutively with no intermittent pause and in random order. One circle was randomly presented for 1s, and the comparison circle for either 1.3s, 1.4s or 1.5s, with two trials for each comparison and with 2.1s response time for each trial. The subjects were told that in this experimental condition indicated by the letter “L” they had to decide which circle stayed on the screen for the longest time by responding with a left-sided button if the red circle, (displayed left), lasted longest, or a right-sided button if the green circle, (displayed right), lasted longest (Figure 8.1).

The TOJ (control) condition was presented identically. The only difference was that these blocks began with the presentation of the number “2” and required subjects to indicate which circle came second using the same response buttons as described above.

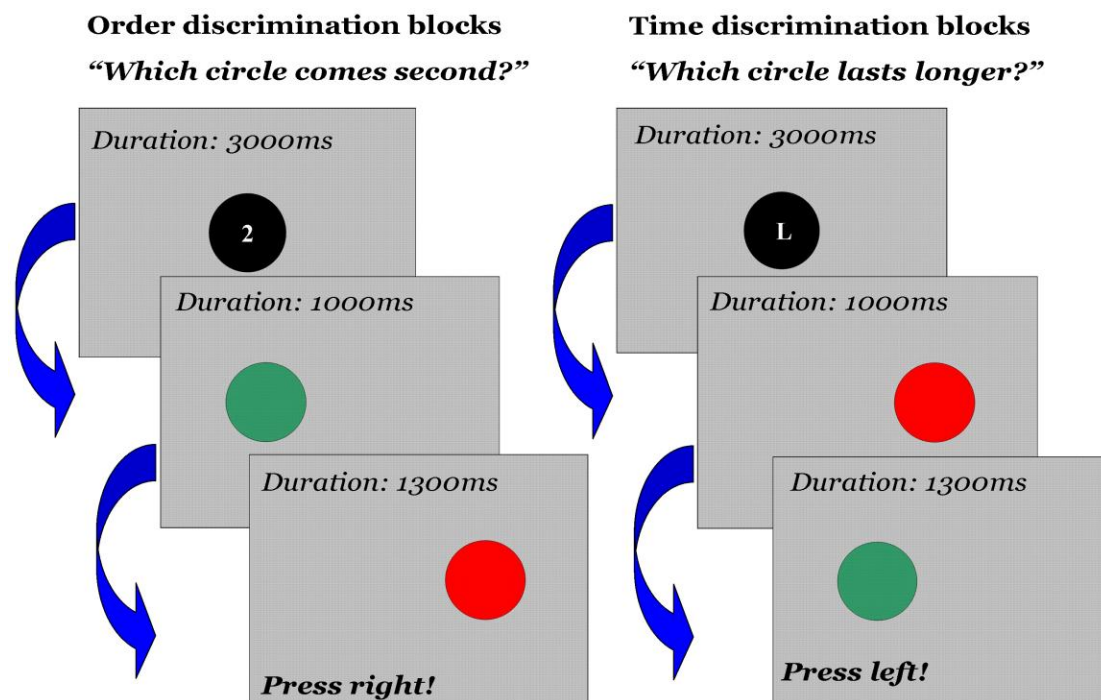


Figure 8.1. Temporal Order Judgement and Time Discrimination conditions. Time discrimination blocks: after the appearance of a cue letter 'L' for 3s, subjects are presented with 6 pairs of red and green coloured circles, which appear consecutively left and right from each other. One of them is randomly presented for a standard duration of 1s, and the comparison circle for either 1,3s, 1,4 or 1,5s. Subjects have to decide which of the two circles had the longer duration, by pressing the left/right button. Temporal order judgement blocks: after the appearance of the cue number '2' for 3s, subjects are presented with the same stimuli, but they have now to indicate which circle came second.

8.2.3. Task performance analysis

Accuracy of TD and TOJ defined by number of errors was analysed by three one-way ANOVA comparing healthy controls and patients under each medication, separately. Within-patients, repeated measures ANOVAs were conducted to compare the effects of medication as well as for the presence of potential practice effects.

8.2.4. MRI Acquisition

Gradient echo echoplanar MR imaging (EPI) data were acquired on a GD Signa 3T Horizon DHx system (General Electric, Milwaukee, WI, USA) at the Centre for Neuroimaging Sciences, Institute of psychiatry, King's College London, UK. A semi-automated quality control procedure ensured consistent image quality (Simmons et al., 1999). A quadrature birdcage head coil was used for RF transmission and reception. In each of 48 non-contiguous planes parallel to the anterior-posterior commissure line 100 T₂*-weighted MR images depicting BOLD (Blood Oxygen Level Dependent) contrast covering the whole brain were acquired with TE=30ms, TR =3s; flip angle =90°, in plane resolution=3.1mm, slice thickness=3.0mm, slice skip = 0.3mm. This EPI dataset provided complete coverage.

We used the non-parametric XBAM software (Brain Image Analysis Unit, 2011) developed at the Institute of Psychiatry, Kings College, London (Brammer et al., 1997; Bullmore et al., 2001; Bullmore, Brammer, et al., 1999) which uses median statistics to control outlier effects and permutation rather than normal theory based inference, recommended for fMRI. Furthermore, the most common test statistic is computed by standardising for individual difference in residual noise before embarking on second level, multi-subject testing using robust permutation-based methods. This allows a mixed effects approach to analysis recommended for fMRI (Thirion et al., 2007)

FMRI data were first processed to minimise motion related artifacts (Bullmore, Brammer, et al., 1999). A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x y and z axes) and translations (in x y and z) that maximised the correlation between the image intensities of the volume in question and the template (rigid body registration). Following realignment, data were then smoothed using a Gaussian filter (FWHM, 7.2mm) to improve the signal to noise characteristics of the images.

After preprocessing, time series analysis for each individual subject was based on a previously published wavelet-based data resampling method for functional MRI data (Bullmore et al., 2001; Bullmore, Suckling, et al., 1999). Briefly, we first convolved the experimental condition with two Poisson model functions (peaking at 4s and 8s) after motion correction, and performed global detrending and spin-excitation history correction. We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ-ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ-ratio for each subject, which were combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data.

After first-level analysis, the individual statistical maps were then normalised into Talairach standard space (Bullmore et al., 2001). A group activation map was then produced for the experimental condition (TD–TOJ) by calculating the median SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). The analysis was then extended from the voxel to the 3D cluster level. An initial voxel-level statistical threshold was first

set to $p < 0.05$ to give maximum sensitivity and to avoid type II errors. 3D clusters were then built from these significant voxels by linking together adjacent voxels into 3D structures. The same process was performed both in the real and in the randomised data. The statistic used for the rest of the process is the cluster mass, which is the sum of the individual voxel statistics over the whole cluster. Cluster mass rather than a cluster extent was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore, Suckling, et al., 1999). The statistical masses from all the 3D clusters were then pooled together to build a null distribution of cluster masses. The cluster mass of any cluster could then be tested against this null distribution. Using this distribution, we set the cluster-level statistical threshold in such a way that the final expected number of type I error 3D clusters was <1 per whole brain.

The necessary combination of voxel and cluster level thresholds is not assumed from theory but rather determined by direct permutation for each data set. In large connected clusters, we identified local maxima that were farther apart than the upper bound of the likely Talairach mapping error (3 voxel radius:10 mm) (Thirion et al., 2007). Voxels were then assigned to the nearest local maximum with a statistic value that exceeded that of the voxels. 3D clusters were constructed from these significant voxels and the mass of the clusters was then tested for significance in such a way as to obtain less than 1 false positive cluster over the whole brain. This combined voxel/cluster tests coupled with permutation testing allow for excellent type I error control at the cluster level (Bullmore, Brammer, et al., 1999; Bullmore, Suckling, et al., 1999). For each analysis, <1 false positive 3D cluster per map was expected at a p -value of <0.05 at the voxel-level and <0.01 at the cluster-level.

For between-group comparisons, a series of three ANOVAs were carried out comparing controls with a) patients on placebo; b) patients on MPH; and c) patients on ATX. For within-group comparisons, a one-way ANOVA was carried out for medication condition: (placebo, MPH, ATX). Statistical measures of BOLD response were then extracted for each participant in each of the clusters of between- and within-group differences and post-hoc analyses were conducted to clarify the direction of the differences. Within patients, repeated measures ANOVAs on the extracted BOLD response measures were conducted to test for potential order effects.

In order to test whether the between-and within-group differences in brain activation were related to performance in all subjects, statistical measures of BOLD

response (SSQ-ratios) were extracted for each participant in each of the clusters of between- and within-group differences for the contrast of TD versus order judgement.

8.3. Results

8.3.1. Task Performance

Time discrimination

One-way ANOVAs showed that healthy controls had significantly lower error rates than boys with ADHD when these were under placebo ($F(1,38)=5$, $p<0.026$) and ATX ($F(1,38)=7$, $p<0.014$), but did not differ from those of ADHD boys when they were under MPH ($F(1,38)=2$, $p<0.16$) (Table 6.2). However, when IQ was used as a covariate, group differences disappeared.

A repeated measures ANOVA comparing errors within children with ADHD under each medication condition was significant ($F(2,38)=4.8$; $p=0.022$), which was due to fewer errors in ADHD patients during the MPH condition relative to placebo (trend level, $p<0.06$) and ATX ($p<0.03$) (Table 8.2).

Temporal Order Judgement

One-way ANOVAs showed no differences between healthy controls and ADHD boys under placebo ($F(1,38)=0$, $p<0.89$), MPH ($F(1,38)=0$, $p<0.87$) and ATX ($F(1,38)=0$, $p<0.55$) (Table 6.2). Differences remained not significant when IQ was used as a covariate.

A repeated measures ANOVA comparing errors within children with ADHD under each medication condition showed no significant drug effect on this condition ($F(2,38)=1$, $p<0.49$) (Table 8.2).

Table 8.2. Performance of healthy controls and children with ADHD under placebo, MPH and ATX during Time Discrimination

Group	% Errors (SD)	
	Time Discrimination	Temporal Order Judgement
Healthy control boys	22 (22)	6 (14)
Boys with ADHD under placebo	40 (29)	6 (9)
Boys with ADHD under MPH	32 (26)	5 (11)
Boys with ADHD under ATX	40 (24)	8 (8)

Note: MPH= Methylphenidate; ATX= Atomoxetine

8.3.2. Brain Activation

8.3.2.1. Motion

Multivariate ANOVA showed no significant group differences between controls and ADHD patients under each drug condition in the extent of mean rotation and translation movement parameters in the 3-dimensional Euclidean space ($F(6,152)=1.5$; $p=0.18$).

8.3.2.2. Within-group activation

During the contrast of TD versus TOJ, healthy control boys showed activation in bilateral IFC, right DLPFC, SMA/ACC, bilateral pre- and post-central gyri and right IPL (Figure 8.2, Table 8.3).

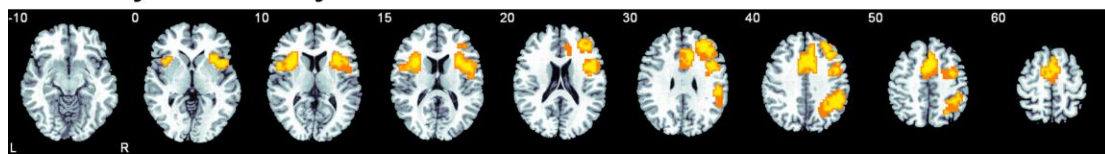
Patients under placebo during TD showed activation in right VMPFC and bilateral IFC, SMA/ACC, striatum and brain stem, right MTG and STG, right IPL and bilateral cerebellum (Figure 8.2, Table 8.3).

When under a single dose of MPH, patients showed activation during the contrast of TD versus TOJ in bilateral IFC and DLPFC, caudate, SMA/ACC and cerebellum, as well as in right lateralised regions including the right MTG and IPL and right cuneus (Figure 8.2, Table 8.3).

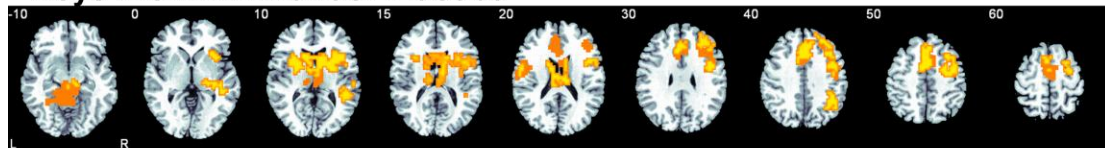
After a single dose of ATX, children with ADHD showed activation during the contrast of TD versus temporal order judgement in bilateral IFC and DLPFC, ACC extending to SMA, right IPL and in bilateral lingual gyrus reaching into cerebellar vermis (Figure 8.2, Table 8.3).

Within-group activations during Time Discrimination Task

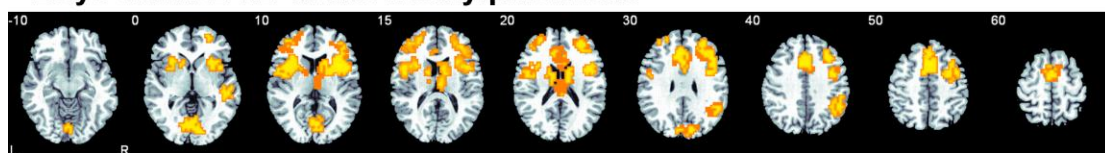
Healthy control boys



Boys with ADHD under Placebo



Boys with ADHD under Methylphenidate



Boys with ADHD under Atomoxetine

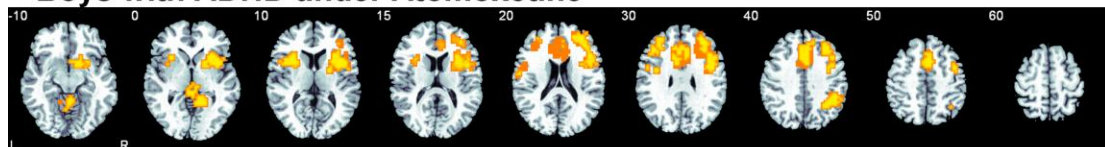


Figure 8.2. Within group activation maps for the Time Discrimination Task. Axial sections showing within-group brain activation for the healthy comparison boys and boys with ADHD under each condition (placebo, MPH, ATX) for the contrast TD-TOJ. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 8.3. Brain Activation within each group

Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	P value
Time discrimination – Temporal Order Judgment Contrast				
Healthy control boys				
R inferior/medial frontal/pre/postcentral gyri/insula	44/45/47/9/10/46/6/4	47; 11; 20	467	<0.001
L inferior frontal/precentral gyri/insula	45/44	-29;22;10	115	0.005
R + L anterior cingulate gyrus/ supplementary motor area	24/32/6	7; 11; 40	352	<0.001
R inferior parietal gyrus	40	51; -37; 33	109	0.007
Boys with ADHD under PLACEBO				
R inferior frontal/precentral gyri/insula/putamen, caudate, thalamus	47/6	40; 18; -4	285	<0.001
R +L anterior cingulate/medial frontal/supplementary motor area	24/32/8/6	43; 7; 33	249	<0.001
L pre/postcentral gyri	6/4	-54; -4; 16	27	0.006
R inferior/medial/superior frontal/premotor gyri	47/44/46/9/8/6	4; 4; 53	298	<0.001
L putamen/caudate/insula	-	-18; 11; 7	30	0.002
R medial/superior temporal gyri/thalamus	21/22/42	47; -33; -3	65	<0.001
R inferior parietal gyrus	40	40; -48; 36	21	0.005
R+L brain stem/cerebellar vermis	-	4; -26; -16	97	<0.001
R+L brain stem/subthalamic nuclei	-	4; -15; -10	36	0.002
L cerebellum	-	-40; -67; -36	18	0.008
Boys with ADHD under MPH				

L medial frontal gyrus	46/10	-47; 41; 10	66	<0.001
L inferior frontoal/precentral gyri/insula/lenticular nucleus	44/45/6	-36; 15; 7	180	<0.001
R inferior/medial/superior frontal/precentral/anterior cingulate gyri/supplementary motor area/lenticulate nucleus/caudate/thalamus	44/45/47/8/9/10/46/6/24/32	4; 30; 33	986	<0.001
L caudate	-	-11; -4; 16	21	0.006
R medial temporal gyrus	21	54; -26; -3	22	0.006
R inferior parietal gyrus	40	47; -44; 40	104	<0.001
R + L cuneus	19	7; -81; 30	35	0.002
L lateral cerebellum/vermis	-	0; -52; -20	29	0.004
R+ L lingual gyrus/cuneus/cerebellum	17/18	4; -67; -4	105	<0.001
Boys with ADHD under ATX				
R inferior/medial/superior frontal/insula/precentral/lenticular nucleus/caudate/nucleus accumbens	44/45/47/9/10/46/6	32; -33; 43	550	<0.001
L medial frontal gyri	9/10/46	-32; 37; 20	58	<0.001
L inferior frontal/precentral gyri/insula/lenticular nucleus	45/6	-29; 15; 7	81	<0.001
L inferior frontal/precentral/postcentral gyri	6/4/44	-54; 0; 20	28	0.005
R + L anterior cingulate gyrus/supplementary motor area	24/32/6	4; 18; 40	291	<0.001
R thalamus	-	7; -18; 0	65	0.002
R inferior parietal gyrus	40	47; -33; 43	77	<0.001
R parahippocampal gyrus	-	18; -44; -3	17	0.006
R + L vermis cerebellum/subthlamic nuclei	-	14; -26; -20	102	<0.001

Note: N voxels = number of voxels. L = left; R = right. The maps are thresholded to give less than 1 Type I3D error cluster per map.

8.3.2.3. ANOVA between-group comparisons of healthy controls and children with ADHD under placebo, MPH or ATX

Controls compared to patients under placebo

Compared to controls, boys with ADHD showed reduced activation under placebo in SMA/ACC, in bilateral IFC, reaching into insula and putamen in the left hemisphere, and right DLPFC. A small cluster in left MFC was enhanced in children with ADHD compared with controls (Figure 8.3, Table 8.4). A negative correlation approaching significance was observed between the number of errors and brain activation within SMA/ACC for all subjects for the comparison between controls and children with ADHD under placebo ($r=-0.28$; $p<0.07$).

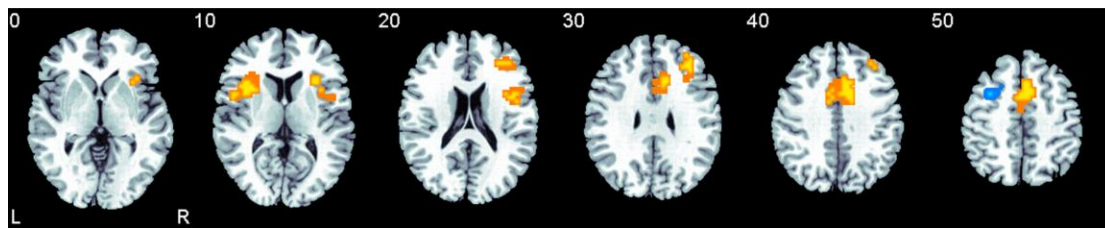
Controls compared to patients under MPH

Under MPH, compared to controls, patients with ADHD only showed reduced activation in the cluster in the ACC but this was reduced in size and no longer included the SMA (Figure 8.3, Table 8.4). No areas of enhanced activation for the ADHD group compared with controls were observed. A significant negative correlation was observed between number of errors and brain activation within SMA for all subjects for the comparison between controls and ADHD patients under MPH ($r=-0.38$, $p<0.01$).

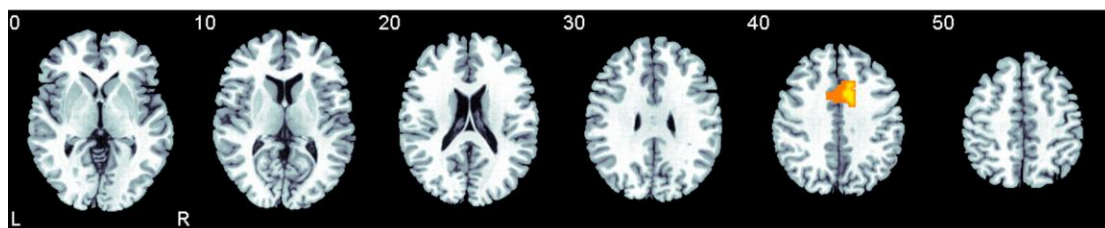
Controls compared to patients under ATX

Under ATX, compared to controls, ADHD boys showed reduced activation in the same regions of left IFC, reaching into insula and SMA/ACC that were reduced under placebo, although both clusters were reduced in size (Figure 8.3, Table 8.4). No areas of enhanced activation for the ADHD group compared to healthy subjects were observed.

Controls versus ADHD placebo



Controls versus ADHD MPH



Controls versus ADHD ATX

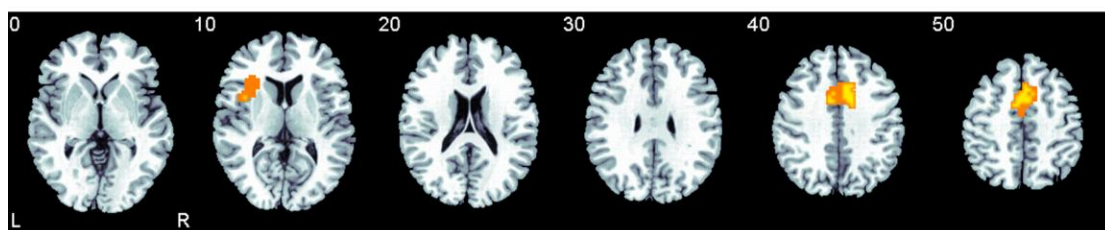


Figure 8.3. Transversal images of the between-group ANOVA comparison between healthy control boys and boys with ADHD on a) placebo b) MPH c) ATX during time discrimination. Statistical threshold selected at $p < 0.05$ for voxel and $p < 0.01$ for cluster levels. Slices are marked with the z-coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

Table 8.4. Between-group ANOVA results showing differences between controls and boys with ADHD under either placebo, MPH, or ATX for the contrast of TD versus order judgement.

Subject Contrast	Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x;y;z)	N of voxels	Cluster P value	Cohen's <i>d</i>
C > ADHD Plac	R + L supplementary motor area/anterior cingulate cortex	32/6	7; 11; 40	116	<0.001	0.64
	R dorsolateral prefrontal cortex	9	36; 37; 33	44	0.008	1.03
	L inferior frontal gyrus, insula, putamen	45/44	-29; 22; 10	42	0.003	0.95
	R inferior frontal gyrus	45/44	47; 11; 20	28	0.007	0.95
	R inferior frontal gyrus, insula	47	40; 22; 0	42	<0.001	0.94
ADHD Plac > C	L superior frontal gyrus	24	-25; 11; 52	24	0.009	1.13
C > ADHD MPH	R + L anterior cingulate cortex	32	7; 11; 40	31	<0.001	1.32
C > ADHD ATX	R + L supplementary motor area /anterior cingulate gyrus	32/6	7; 11; 40	94	<0.001	0.86
	L Inferior frontal gyrus, insula	45	-29;22;10	19	<0.001	0.87

Note: N voxels = number of voxels. L = left; R = right. The maps are thresholded to give less than 1 Type I3D error cluster per map.

8.3.2.4. Significance of the “normalization” and “laterality” effects

We wanted to analyze the significance of the “normalization” effects observed in the between-groups fMRI analysis. Given that the data of the healthy control group were identical across the different case-control comparisons, non-parametric Friedman tests were conducted only within patients to identify whether there were significant differences in brain activation under each drug condition in each of those clusters where the case-control contrasts showed “normalization” effects.

None of the clusters of activation showed significant differences between brain activation under each drug condition (Right IFC/insula: BOLD Placebo: 0.029; BOLD MPH: 0.076; BOLD ATX: 0.047; χ^2 (2, N=20)=1.20, $p < 0.55$; right IFC: BOLD Placebo: 0.039; BOLD MPH: 0.046; BOLD ATX: 0.044; χ^2 (2, N=20)=0.90, $p < 0.64$; right DLPFC: BOLD Placebo: 0.036; BOLD MPH: 0.061; BOLD ATX: 0.062; χ^2 (2, N=20)=2.70, $p < 0.26$; SMA/ACC: BOLD Placebo: 0.038; BOLD MPH: 0.061; BOLD ATX: 0.060; χ^2 (2, N=20)=0.10; $p < 0.95$) although they were all in the right direction, suggestive of only “relative” or “moderate” normalisation effects. However, in the cluster comprising the left IFC/putamen, there was a trend for significant differences in activation (BOLD placebo: 0.042; BOLD MPH: 0.091; BOLD ATX: 0.072; χ^2 (2, N=20)=4.30, $p < 0.11$), which, as shown by the post-hoc Wilcoxon test, was due to the differences between brain activation under placebo relative to MPH ($p < 0.009$) and at a trend level between placebo and ATX ($p < 0.057$).

In order to test for the significance of the laterality effects on the BOLD signal changes observed in the right IFC/insula and left IFC under MPH and ATX, we conducted a repeated measures analysis within patients with laterality (2 levels: right IFC, left IFC) and drug condition (3 levels: placebo, MPH and ATX) as within-subjects factors. There were no significant laterality x drug interaction effects ($F(2,38)=0.11$, $p < 0.90$).

8.3.2.5. Within-patients comparison between placebo, MPH and ATX

Given the reduced activation in prefrontal regions and SMA/ACC, we tested for significant upregulation effects of both drugs in prefrontal regions and SMA/ACC. For this purpose, the Talairach Client (Lancaster et al., 1997; Lancaster et al., 2000) was used to define a mask of the frontal lobe, which also included the ACC/SMA,

restricting the analysis to those voxels present in the mask. Repeated measures ANOVA showed a significant effect of drug condition in one cluster of activation comprising the SMA/ACC (105 voxels, peak Talairach coordinates (x;y;z):0;15;46; BA 6/32; $p < 0.01$) due to enhanced activation in this cluster when ADHD boys were under MPH relative to ATX ($p < 0.05$, one-tailed) and at a trend level, also relative to placebo ($p < 0.07$, one-tailed) (Figure 8.4). No significant correlations were observed between TD errors and activation differences between any drug conditions.

ANOVA comparisons between children with ADHD under placebo, Methylphenidate and Atomoxetine conditions

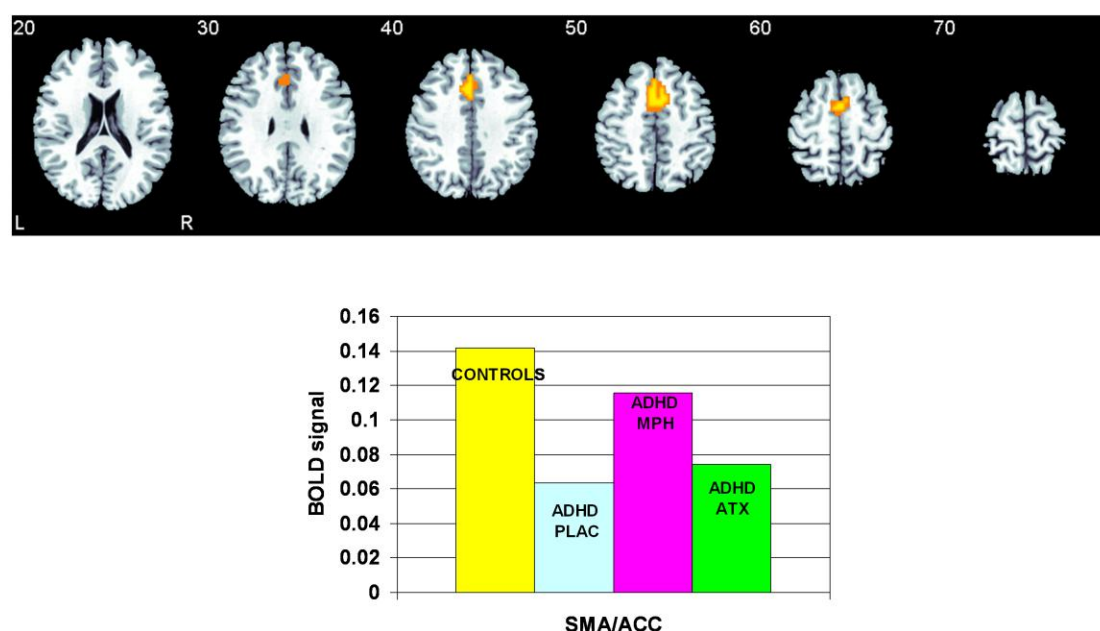


Figure 8.4. Transversal images of the within-group ANOVA analysis for the TD-TOJ contrast. The figure shows the areas of increased brain activation in boys with ADHD with an acute dose of MPH compared with placebo and ATX during time discrimination contrasted with order judgement. Statistical threshold set at $p < 0.05$ for voxel- and $p < 0.01$ for cluster-wise analysis. Slices are marked with the z coordinate as distance in millimetres from the anterior-posterior commissure. Mean statistical BOLD response is shown for each drug condition within SMA/ACC (Supplementary Motor Area/Anterior Cingulate). The bar chart shows the SSQs for all the groups (healthy controls, ADHD boys under placebo, ADHD boys under Methylphenidate and ADHD boys under Atomoxetine).

Despite the randomised controlled design, to exclude the possibility that order effects may have accounted for some of the differences in performance or brain activation within patients or between cases and controls, a repeated measures ANOVA within patients analysis was conducted. There were no significant practice effects on performance or BOLD response in the clusters of activation differences in the within group analyses.

8.4. Discussion

This study demonstrates a significant drug-specific effect of MPH relative to placebo and ATX on performance and underlying networks of TD in children with ADHD. Relative to controls, boys with ADHD had reduced activation in typical areas of time perception of SMA/ACC, bilateral IFC, left insula and putamen, and right DLPFC. Within patients, MPH relative to ATX and placebo significantly decreased TD errors and upregulated SMA/ACC. Case-control comparisons showed that MPH had drug-specific moderate normalisation effects of the reduced activation when under placebo in SMA as well as in left IFC and insula. Shared effects were also observed, however, with both drugs reducing the right frontal underactivation.

ADHD patients had reduced activation under placebo relative to controls in key regions associated with temporal perception, particularly the SMA reaching into ACC, as well as bilateral IFC, insula and reaching into left putamen, which are typical areas of time perception in adults (Rubia & Smith, 2004; Smith et al., 2003; Wiener et al., 2010; Wittmann & van Wassenhove, 2009) and adolescents (Smith et al., 2011). The SMA is a key area for TD, frequently co-activated with ACC, insula and left IFC, although right IFC is more commonly thought to mediate attention to time (Rubia, 2006; Wiener et al., 2010). The association between SMA and TD errors in ADHD patients is supported in this study by the correlation between SMA/ACC and percentage of TD errors across all subjects, which replicates earlier correlation findings between underactivation in this region and inaccuracy in ADHD (Smith et al., 2008). Left and right IFC and DLPFC deficits during the same task have also previously been observed in this patient group (Rubia, Halari, Christakou, et al., 2009; Smith et al., 2008)

The finding of a significant upregulation effect of MPH on SMA/ACC and the moderate normalisation effect on SMA, bilateral inferior and dorso-lateral prefronto-striatal underactivation in ADHD boys during placebo extends previous findings of neural upregulation and normalisation with MPH of these key regional underactivations during the same TD task (Rubia, Halari, Christakou, et al., 2009). The same brain areas were also found to be normalized with a single dose of MPH during other tasks of cognitive control (Rubia, Halari, Mohammad, et al., 2011).

The novelty of these findings is that we show for the first time that only MPH upregulated and moderately normalised SMA activation, while it also completely normalized left IFC/putamen activation relative to ATX, while the moderate drug

normalisation effects on right fronto-insular underactivation are shared. The drug-specific normalisation effects of MPH on left putamen are in line with its key role during fine temporal discrimination processes (Rubia, 2006; Wiener et al., 2010) and with the modulatory effects shown by a single dose of MPH in basal ganglia in medication-naïve children with ADHD (Rubia, Halari, Christakou, et al., 2009). The moderate normalisation of right IFC activation during ATX extends previous evidence for upregulation of this region in healthy adults (Chamberlain et al., 2009), showing for the first time that ATX also upregulates right lateral frontal areas in children with ADHD, suggesting the same mechanism of action in healthy subjects as well as ADHD patients.

The moderate normalisation effects of ATX on right but not left-sided IFC/insula in children with ADHD suggest that ATX has stronger effects on right hemispheric, noradrenergically modulated regions than left-hemispheric frontal regions (Chamberlain et al., 2009; Lawrence et al., 2003; Malone, Kershner, & Swanson, 1994). However, ATX showed some effects on the left IFC activation, with reduced size of the activation cluster and trend-level normalization effects. The bilateral frontal upregulation effects under MPH may reflect stronger left-hemispheric upregulation effects of MPH rather than ATX (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009). Previous evidence shows increased levels of DA within subcortical structures in the left hemisphere (Flor-Henry, 1986) underpinning the proposal that this side of the brain may be associated with dopaminergic fronto-striatal pathways of arousal (Malone et al., 1994). Consequently, stimulants such as MPH may have a stronger effect than ATX on left hemispheric mesolimbic dopaminergic pathways between the basal ganglia and left frontal regions and SMA.

The drug-specific improvement of performance deficits in ADHD by MPH, but not ATX, could potentially be explained by the fact that MPH had a more global effect on the different components of TD neural networks. Thus, MPH showed upregulation and moderate normalisation effects on SMA activation, and moderate normalisation effects in left IFC/insula and putamen activation, considered as a key region of time estimation, together with the SMA (Rubia, 2006; Rubia & Smith, 2004; Wiener et al.). The moderate normalisation effects on right frontal activation with both drugs may also reflect an enhancement of more generic catecholamine-mediated attention functions that are co-measured in timing functions (Berridge et al., 2006;

Rubia, 2006; Wiener et al., 2010). In frontal regions, MPH upregulates not only DA but also NE (Balcioglu et al., 2009; Berridge et al., 2006; Hannestad et al., 2010), via reuptake inhibition of NETs which clear up both DA and NE (Moron et al., 2002; Yamamoto & Novotney, 1998) and effects may therefore have been similar with both drugs, mediated by enhanced catecholamine neurotransmission.

The moderate normalisation of the underlying networks of left insula, IFC, putamen and the SMA with MPH are in line with behavioural evidence which shows consistently positive effects of dopamine-agonists on TD in humans (Rubia, 2006), while there is only scarce evidence for the relationship between NE agonists and TD functions in healthy adults (Rammsayer, Hennig, Haag, & Lange, 2001). The findings also suggest that DA may play a more crucial role in SMA within the context of TD, and are consistent with the presence of DAT (Ciliax et al., 1999) relative to the scarce NET presence (Smith, Beveridge, & Porrino, 2006) in the SMA. The upregulating effects on the SMA/ACC may hence have been mediated by meso-limbic dopaminergic pathways between the striatum and the SMA (Akkal, Dum, & Strick, 2007), operating within a wider hypothesized timekeeping circuit (Stevens, Kiehl, Pearson, & Calhoun, 2007) involving bilateral IFC, insula and the SMA. Parkinsonism patients with striatal dopamine deficiencies consistently show TD deficits (Artieda, Pastor, Lacruz, & Obeso, 1992) and underactivation in the SMA which receives dopaminergic projections from the striatum (Akkal et al., 2007; Galvan & Wichmann, 2008). While poor function is consistently normalized with L-DOPA (Rascol et al., 1994) and other DA agonists (Le & Jankovic, 2001), there are less consistent findings with NE agonists (Jenner, Sheehy, & Marsden, 1983), further supporting a predominant role of DA in SMA function. Therefore, MPH seems to have stronger effects on time discrimination networks, with more pronounced normalisation effects than those of ATX, which are likely to be mediated by dopaminergic effects.

This study is strengthened by the recruitment of medication-naïve children with ADHD thus controlling for the confounding effects of long-term stimulant medication on brain activation. A limitation is that for ethical reasons, controls were only tested once, while patients were tested three times. However, for the within subjects analysis, potential practice effects were controlled for by the counterbalanced design and furthermore, no practice effects were observed. This suggests that is unlikely that practice effects have contributed to performance or brain activation

differences between patients and controls. However, such assumption must be made with caution, as we could only test for potential order effects within subjects. Even then, this was conducted with a very small sample, and therefore the power to detect potential order effects is severely reduced. Furthermore, given the reduced number of participants on each condition, it was not possible to test for potential sequence effects derived from the randomisation order. This means that the administration of the drug conditions in a determined randomization order may have enhanced or reduced their effects. Further studies with sufficiently large samples should be conducted to rule out this possibility. In addition, the wider age range of the healthy control group relative to the ADHD boys may have affected the results by widening the between-groups differences in a disorder that has shown to be associated with neurodevelopmental delay (Rubia, 2007; Shaw et al., 2007; Shaw et al., 2012). Therefore, future studies should ideally include more closely age-matched groups.

An important limitation is the investigation of acute rather than chronic doses of each drug. As a single dose challenge, this design reduces long-term confounds such as symptomatic improvement, side effects or chronic effects on brain activation. However, it may be biased towards MPH effects, given that they are clinically relatively immediate, while ATX is slower to act, with maximum clinical efficacy after 4-6 weeks of chronic administration (Montoya et al., 2009). Future studies should compare the long-term effects of both drugs on brain function to accommodate differences in time to maximum efficacy.

To conclude, to our knowledge this is the first study to directly compare neurofunctional effects of ATX and MPH in children with ADHD. We observed both drug-specific and shared effects of single doses of ATX and MPH on abnormal time estimation networks in ADHD. While MPH had a drug-specific upregulation and moderate normalising effect on SMA underactivation, both drugs showed moderate normalisation effects of lateral frontal underactivations, albeit these were stronger for MPH. The drug-specific upregulation findings of MPH on performance and error-correlated SMA activation strengthen the association between abnormalities in dopaminergic neurotransmission, ADHD and temporal processing (Rubia, Halari, Christakou, et al., 2009).

CHAPTER 9. GENERAL DISCUSSION

9.1. Summary of the results

MPH and ATX are currently the two most commonly prescribed drugs for the treatment of ADHD symptoms. However, their mechanisms of action have remained poorly understood and their compared effects on brain activation in ADHD patients are as yet unexplored. This thesis has compared, for the first time, the effects of single dose challenges of MPH and ATX on brain activation in ADHD. To do so, medication-naïve ADHD boys were recruited from clinics and scanned after a single dose of each drug. They performed cognitive tasks in which, relative to healthy boys, they typically present with performance deficits and abnormal brain activation. The results show that single doses of either MPH or ATX had both drug-specific and shared effects on their performance and brain activation which were, however, highly task-dependent.

During WM, children with ADHD under placebo showed impaired performance, with better performance than controls in the most simple 1-Back condition, but increased errors in the more difficult 2-Back and 3-Back conditions. ADHD boys under placebo showed reduced activation relative to healthy controls in bilateral DLPFC. Activation in the right DLPFC was negatively associated with errors both in healthy controls and at a trend level also in patients under placebo, supporting the key role of this region in WM processes. ATX showed drug-specific effects in the right DLPFC, which was upregulated in activation by ATX relative to MPH, within patients. Furthermore, relative to MPH, only ATX significantly normalised the underactivation observed in the same region when patients were under placebo relative to healthy control boys. On the other hand, MPH showed WM load-dependent drug-specific effects during the WM task. Only MPH upregulated left IFC activation, both within subjects as well as relative to healthy control boys, but only during the 2-Back condition. Thus, the differential drug-specific normalisation and upregulation effects in right DLPFC underactivation in patients after ATX administration relative to controls and the upregulated activation in left IFC in patients after MPH are in contrast with the initial hypothesis of the study. We hypothesised that both drugs would modulate brain activation in PFC and that MPH would additionally do so in basal ganglia activation. WM is known to be mediated by DA and NE in PFC (Gamo et al., 2010). Both MPH and ATX enhance NE and DA in PFC (Berridge et al., 2006;

Bymaster et al., 2002; Swanson et al., 2006). MPH has shown to upregulate PFC and striatum activation in children with ADHD during WM (Prehn-Kristensen et al., 2011; Sheridan et al., 2010). Dopamine has been shown to play a key role in WM processes (Chudasama & Robbins, 2004; Cools & D'Esposito, 2011; Landau et al., 2009). However, WM has also been shown to be sensitive to noradrenergic manipulations (Chamberlain, Muller, Blackwell, Robbins, et al., 2006). The findings suggest that ATX had more prominently right-hemispheric upregulation and normalisation effects in the key WM area of DLPFC, while MPH showed left-hemispheric drug-specific effects in IFC. Both MPH and ATX may have had similar effects on DA and NE networks, given that both drugs enhance DA and NE in PFC (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006). Alternatively, the results suggest that the drug-specific effects during the WM task were differentially lateralised in prefrontal regions, consistent with evidence for a hemispheric bias of dopaminergic and noradrenergic systems (Flor-Henry, 1986; Glick et al., 1982; Tucker & Williamson, 1984), which should however be further investigated in future studies.

Shared effects during WM included the normalisation of the impaired performance of children with ADHD under placebo relative to controls. At the brain activation level, both drugs abnormally enhanced activation in fronto-STG-striatal regions relative to controls. Furthermore, both drugs enhanced WM load-dependent deactivation of the DMN relative to healthy controls. The presumably compensatory role of the enhanced fronto-STG-striatal activation was supported by its association with performance and, in the case of MPH, by its negative association with the reduced activation in DLPFC. However, even when these effects were shared they presented with some differences. The enhanced activation in boys with ADHD relative to controls in fronto-STG-striatal regions reached the right IFC only when subjects were under a single dose of ATX but not when they were under MPH. Similarly, although both drugs shared enhanced deactivation effects in the DMN, the location and temporal pattern of these effects differed depending on the drug. When under MPH, these effects were observed only during the 2-Back condition, were located in bilateral occipital regions reaching into precuneus, and were negatively associated with the drug-specific enhanced activation in left IFC during the same 2-Back condition as well as with improved performance. On the other hand, the

deactivation effect of ATX was progressively stronger with increased WM-load and localised in midline ACC-PCC regions.

During the motor response inhibition task, medication-naïve children with ADHD relative to controls showed reduced activation in bilateral VLPFC, in right cerebellum reaching into occipital regions, as well as in left temporo-parietal cortices. During the SST, only MPH showed drug-specific effects. Behaviourally, only MPH sped up inhibitory processes in ADHD boys, which exceeded that of healthy control boys. At the brain activation level, only MPH showed significant drug-specific effects on right VLPFC-cerebellar inhibitory networks. Thus, only MPH significantly normalised the reduced activation when under placebo relative to healthy boys in right VLPFC, as well as in right anterior cerebellum extending to occipital areas. As during WM, only MPH showed some drug-specific effects during this task, which were more prominently left-lateralised. Thus, during the motor execution component of the SST, only MPH upregulated brain activation relative to healthy boys in left basal ganglia reaching into left IFC, in left premotor regions and in SMA/ACC.

Although ATX showed normalisation effects in right VLPFC and cerebellar regions during the SST, these effects were moderate and not statistically significant. Whether these would be stronger under prolonged administration of ATX or different dosages of the drug needs to be further studied. ATX only showed significant effects that were shared with those of MPH. Thus, both drugs normalised the underactivation observed under placebo relative to healthy boys in left VLPFC. Although this region has shown to be highly relevant for motor response inhibition processes (Nee et al., 2007; Swick et al., 2008), it has also shown to be involved in performance monitoring processes (Derrfuss et al., 2005). Furthermore, previous evidence in medication-naïve ADHD boys during the same SST task used here showed upregulation and normalisation of left IFC activation after a single dose of MPH in children with ADHD (Rubia, Halari, Mohammad, et al., 2011). Hence, although the effects on left VLPFC activation may be due to upregulation of motor inhibition neural networks by both drugs, we hypothesised that these effects were due to improved performance monitoring processes.

Thus, the results from the SST are partially in line with the initial hypotheses of the study. In healthy adults, a single dose of ATX has shown upregulation effects in the key inhibitory area of right IFC during a Stop task (Chamberlain et al., 2009). MPH has also been shown to have upregulation effects on prefrontal and striatal brain

activation within children with ADHD during motor inhibition tasks (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998). The left IFC has also shown its crucial role during motor inhibition (Nee et al., 2007; Swick et al., 2008). Based on this evidence, we expected that a single dose of ATX and MPH would show comparable effects in inhibitory regions including the right but also the left IFC, with perhaps slightly stronger effects for ATX given the evidence supporting the relevance of NE during motor inhibition processes as measured by the SST (Bari et al., 2009; Eagle et al., 2008). We also hypothesised that only MPH would show upregulation and normalisation on brain activation in the basal ganglia, given that only MPH and not ATX have been shown to have dopaminergic effects in the striatum (Bymaster et al., 2002; Swanson et al., 2006; Volkow, Wang, Fowler, Gatley, et al., 1998). Although we find shared normalisation effects in left VLPFC by both drugs, only MPH showed significant normalisation and upregulation effects in right VLPFC and cerebellar regions.

Finally, during TD, medication-naïve boys with ADHD under placebo showed reduced activation relative to healthy boys in key TD regions including bilateral VLPFC and ACC/SMA. As in the SST, only MPH showed drug-specific effects. Behaviourally, only MPH relative to ATX and placebo improved performance in the task. At the brain activation level, only MPH showed upregulation effects in SMA and ACC, with additional drug-specific moderate normalisation effects in SMA. The shared effects during this task were located in the VLPFC: on the right VLPFC, both drugs showed moderate normalisation of the underactivation of this area under placebo relative to controls, whereas on the left VLPFC both drugs showed normalisation effects, although only when patients were under MPH the underactivation observed when patients were under placebo relative to controls was completely normalised. Our findings were therefore partially consistent with the initial hypothesis of the study. Previous evidence has shown that a single dose of MPH had normalisation and upregulation effects on key regions for TD, including lateral prefrontal regions, basal ganglia, ACC and cerebellum (Rubia, Halari, Christakou, et al., 2009). Furthermore, TD is known to be most prominently dopaminergically innervated and has been shown to be sensitive to dopaminergic manipulations (Baldwin et al., 2004; Ben-Pazi et al., 2006; Rammsayer, 1999; Rubia, 2006; Rubia, Halari, Christakou, et al., 2009; Rubia, Noorloos, et al., 2003; Smith et al., 2003). Thus, we hypothesised that a single dose of MPH would have drug-specific

effects on in bilateral prefrontal and striatal regions, ACC and cerebellum. The results are therefore mostly in line with the initial hypotheses of drug-specific normalisation and upregulation effects of MPH on brain activation in bilateral IFC, striatal and SMA/ACC regions. However, we did not expect the shared moderate normalisation effects of ATX in VLPFC, which may have been due to its effects on both DA and NE on prefrontal regions (Bymaster et al., 2002).

Although these results have been discussed separately in Chapters 6-8, they will be more globally discussed here to arrive to general conclusions on the compared effects of both drugs.

9.2. Task-specific effects

The findings of task-specific drug effects are the most relevant of this study, given their potential implication in the future development of individually tailored treatments for ADHD. A potential explanation for these task-dependent effects may be the inverted-U mode of functioning observed for both noradrenergic and dopaminergic systems. Too low or too high levels of DA or NE have been shown to impair cognitive function (Arnsten, 2009; Berridge et al., 2011; Robbins, 2010), and different levels of DA and NE are required by different cognitive functions (Cools & D'Esposito, 2011; Robbins, 2010).

Hence, the administration of MPH during tasks that have a strong dopaminergic innervation, such as the TD task or the motor execution component of the SST, may have allowed for the neural systems to achieve more adequate dopaminergic levels, needed to perform those tasks. On the other hand, the dopaminergic increase after a single dose of MPH during the WM task may have exceeded the necessary dopaminergic tone in fronto-striatal regions to be able to perform during the most difficult condition of the task, due to its impact on the flexibility-stability trade-off in fronto-striatal networks. The upregulation of the dopaminergic system would have stimulated prefrontal D1 receptors in excess, suppressing firing to relevant and irrelevant stimuli, while it would have engaged D2 striatal receptors thus facilitating the rapid updating of information (Cools & D'Esposito, 2011). Thus, the enhanced dopaminergic tone in the striatum may have facilitated this rapid updating and improved performance during the 2-Back condition, but not during 3-Back condition, whose higher WM load requires longer stability of

the representations in WM and which may require only moderate dopaminergic levels of DA in prefrontal regions.

As described in the previous section, we expected comparable effects for ATX and MPH during the SST. Both drugs showed normalisation effects of the underactivation in ADHD boys under placebo, relative to controls, in the left VLPFC. Activation in this region may be associated to improved inhibitory function, given the evidence for its role during motor response inhibition processes (Nee et al., 2007; Swick et al., 2008). However, activation in this region was not associated with SSRT in patients under either drug condition or in healthy boys. On the other hand, there is evidence for a) the involvement of this region on performance monitoring processes (Derrfuss et al., 2005); b) its stronger upregulation/normalisation as part of performance monitoring networks after a single dose of MPH in children with ADHD (Rubia, Halari, Mohammad, et al., 2011) and c) its upregulation in healthy adults after a single dose of ATX during error monitoring processes (Graf et al., 2011). Thus, we hypothesised that these effects were due to improved performance monitoring processes.

However, while ATX showed only moderate normalisation effects in right VLPFC and cerebellar/occipital regions, MPH showed drug-specific normalisation and upregulation effects on right VLPFC and cerebellar regions, which furthermore were associated with improved SSRT performance and hence directly involved in motor inhibition speed.

The difference between the present findings of no direct upregulation and only a moderate normalisation effect on right VLPFC and those from Chamberlain et al (Chamberlain et al., 2009), where a single dose of ATX showed a direct upregulation effect on this region, may be due to differences in ATX dosages, sample characteristics (healthy adults versus children with ADHD) or a combination of both factors. While in the present study the dose of ATX was weight-adjusted (1mg/kg), Chamberlain et al (Chamberlain et al., 2009) administered a fixed 40 mg dose, which for an adult may have resulted in lower doses than the ones we administered. If we consider an average male adult may weight approximately 70kg, a 40mg dose would be equivalent to a weight-adjusted dose of 0.57 mg/kg. Furthermore, children with ADHD may show reduced function of the NE system, which may have not been adequately modulated during motor response inhibition by a single dose of ATX, perhaps due to different doses or repeated administration being required. On the other

hand a single (and comparatively lower) dose of ATX, as the dose administered by Chamberlain et al, may have been enough to upregulate activation in the key motor inhibition region of right IFC in healthy adults with adequately functioning NE systems. Also using a single dose of MPH, studies in healthy adults have shown different effects than those in children with ADHD. Thus, fMRI studies have shown that while MPH typically enhances activation in prefrontal and striatal regions during motor inhibition in ADHD patients (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998), it has been shown to reduce activation in right IFC during successful inhibition in healthy adults (Pauls et al., 2012). Hence, the effects of single doses of MPH and ATX may differ in paediatric patients and healthy adults, potentially due to the presence or absence of dysfunctional catecholaminergic systems.

Another potential explanation is that at higher doses, ATX may act on performance monitoring networks and not on motor inhibition networks. Thus, the dose of ATX administered in the present study may have been too high to adequately modulate brain activation in regions involved in motor inhibition processes. This would be in line with a recent study in healthy adults where a single dose of 80 mg of ATX showed upregulation effects during a combined GNG/Flanker task on performance monitoring networks including bilateral IFC, while impairing inhibition performance during incongruent (but not during congruent) NoGo trials (Graf et al., 2011).

Thus, the dose of ATX administered in the present study may have been too high to adequately modulate key motor inhibition regions, but may have shown the effects of ATX on performance monitoring networks. The non-significant normalisation effects of a single dose of ATX on right VLPFC and cerebellar/occipital activation would support this. On the other hand, the dose of MPH may have been more adequate to show its beneficial effects on brain activation during motor inhibition, which may have been partially due to its effects on noradrenergic receptors (Berridge & Devilbiss, 2011).

Furthermore, it is possible that prolonged administration of ATX may have also resulted in significant results, given that ATX takes at least 4 weeks to significantly improve symptoms and 12 weeks to reach maximal clinical efficacy (Montoya et al., 2009). ATX showed moderate normalisation effects on right VLPFC activation, which were not statistically significant. Whether this moderate effect may

become stronger after prolonged administration or at different doses merits further investigation. Hence, studies on the compared effects of different doses and prolonged administration of both drugs would extend these findings.

However, it is important to note that an alternative explanation is that the effects of both drugs are due to their action on both DA and NE systems, given that both MPH and ATX enhance DA and NE in prefrontal regions (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006) and that MPH has been shown to block both DAT and NET (Hannestad et al., 2010; Volkow, Wang, Fowler, Gatley, et al., 1998). It may therefore be that the moderate effects shown by a single dose of ATX on right VLPFC and cerebellar activation may be due to its effects on both DA and NE, and that these moderate effects of ATX would have been significant at different doses or prolonged administration.

We expected MPH to show drug-specific effects on the basal ganglia across tasks, given its effects on striatal DA where it significantly blocks the DAT (Bymaster et al., 2002; Volkow, Wang, Fowler, Gatley, et al., 1998). This effect has not been reported for ATX (Bymaster et al., 2002; Swanson et al., 2006).

In line with this hypothesis, we observed moderate normalisation effects of MPH on left putamen activation during the TD task. These effects are in line with the key role of the basal ganglia during fine temporal discrimination processes (Rubia, 2006; Rubia & Smith, 2004; Wiener et al., 2010) and with the modulatory effects shown by a single dose of MPH in basal ganglia in medication-naïve children with ADHD during the same task (Rubia, Halari, Christakou, et al., 2009). However, we did not observe the expected effects of MPH in basal ganglia during the SST, which contrasts with previous evidence of modulatory effects of MPH on brain activation in basal ganglia not only during motor response inhibition (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998), TD (Rubia, Halari, Christakou, et al., 2009) or WM (Prehn-Kristensen et al., 2011; Sheridan et al., 2010), but also during other tasks of cognitive control (Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Cubillo, et al., 2009; Shafritz et al., 2004).

However, we observed drug-specific effects of MPH on basal ganglia during the motor execution component of the SST. Although not hypothesised, these effects are not surprising, given the key role of the basal ganglia within neural motor circuits (Alexander, DeLong, & Strick, 1986).

Unexpectedly, we observed shared enhancing effects for both drugs during WM in fronto-STG-striatal regions, including the thalamus. While the upregulation effects of MPH may be due to its direct dopaminergic effect in the basal ganglia, the unexpected striatal effects of ATX may be due to direct noradrenergic effects on frontal and thalamic activation, which may have indirectly enhanced striatal activation (Easton et al., 2007; Niiijima et al., 2010).

A potential explanation for the lack of expected effects of MPH on basal ganglia during the SST task is that children with ADHD did not show reduced activation in basal ganglia during the SST, and therefore the effects of MPH may have not been observed because the basal ganglia activation was already optimal and normal. This would be in line with the evidence that we observed some striatal normalisation effects in TD, where in fact the basal ganglia were decreased in activation under placebo. Also, we did find upregulation effects on basal ganglia during motor execution and WM processes. Thus, MPH may have also had an upregulation effect on fronto-striatal motor response inhibition neural networks, but only on those regions where patients showed underactivation relative to controls when under placebo.

Thus, the results highlight the need for studies focused on several aspects. On the one hand, studies are needed to identify the effects of different doses of MPH and ATX on different cognitive functions and the underlying brain activation. Furthermore, the results of the present study are suggestive of the potential benefits of one of the drugs over the other depending on the cognitive function. Thus, while MPH would be better for those patients presenting with TD, motor inhibition or motor execution deficits, ATX would be better suited for those cases presenting with WM problems. However, because these drugs are administered not on a single dose basis but over prolonged periods of time, these results can only be taken as a first suggestion on the differential positive effects of both compounds on cognitive functions and brain activation and need to be confirmed with long-term studies. Additionally, studies on the compared effects of different doses of ATX and MPH would help to determine whether the moderate and non-significant effects of ATX in right VLPFC and cerebellar regions during the SST and in right IFC during the TD become significant at different doses or with longer-term administration given the different time course of the drugs to reach clinical efficacy (Greenhill et al., 2001; Montoya et al., 2009). Furthermore, studies focused on the compared effects of both

drugs on a wider range of executive and non-executive tasks, and over a longer time period, would help to determine whether these task-specific effects can be observed in other cognitive tasks and in the underlying neural networks, or whether these modulatory effects persist over time. Finally, given the evidence for a dissociation of the cognitive and behavioural effects of MPH (Sprague & Sleator, 1977; Tannock, Schachar, et al., 1995), only longitudinal studies will be able to shed some light on the potential association between different dosages, the long-term task-specific effects of the drugs on cognition and brain activation, and their potential association with symptomatic and behavioural improvement.

9.3. Drug-specific effects

As mentioned above, both MPH and ATX showed drug-specific task-dependent effects.

Only MPH sped up inhibitory processes, which exceeded that of healthy controls, during the SST. Although both MPH and ATX normalised the reduced activation in right VLPFC, cerebellum and occipital regions during motor response inhibition processes, these effects were only significant for MPH. This is in line with previous studies where single doses of MPH in children with ADHD normalised and upregulated activation in frontal and cerebellar regions underlying inhibitory processes (Epstein et al., 2007; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998). The findings are also in line with a recent neuropsychological study, which showed that only a single dose challenge of MPH, and not of ATX, improved performance during the Stop task in healthy adults (Nandam et al., 2011). Thus, taken together, and as discussed in Chapter 6, the findings are suggestive of a stronger effect of MPH relative to ATX in typical motor response inhibition networks.

However, and as mentioned in the previous section, the moderate effects of ATX in right VLPFC and cerebellar regions during motor inhibition may have been influenced by the single dose administration, and may require prolonged administration to become significant given that it reaches maximal clinical efficacy after 12 weeks of treatment (Montoya et al., 2009). Alternatively, these moderate effects may have become significant after a different dose of ATX. Therefore, to clarify these aspects, studies on the compared effects of both drugs after prolonged administration and at different dosages are needed.

During the TD task, only MPH reduced the number of errors within subjects relative to placebo and ATX. In the ACC/SMA, MPH showed upregulation effects within subjects and normalised the underactivation observed in SMA when patients were under placebo relative to controls. It is interesting that only MPH showed drug-specific effects on brain activation in these regions across tasks, as only MPH enhanced activation in SMA/ACC both within patients and in patients relative to healthy control boys during motor execution. Thus, these findings are in line with 1) the hypothesised drug-specific enhancing effects of MPH on SMA/ACC during TD; 2) with previous studies showing upregulation and normalisation effects of a single dose of MPH in children with ADHD in SMA/ACC during both TD (Rubia, Halari, Christakou, et al., 2009) and other cognitive control tasks (Rubia, Halari, Mohammad, et al., 2011); 3) with the known DAT distribution in sensorimotor regions (Ciliax et al., 1999) and 4) the dopaminergic innervation of both motor execution (Haber, 2003; Monchi et al., 2006) and TD processes (Rammsayer, 1999; Rubia, 2006; Wiener et al., 2010).

The compared apparent lateralisation of the drug-specific effects shown by the two compounds is highly interesting. During WM, while MPH showed drug-specific left lateralised effects, the drug-specific effects of ATX were right lateralised.

Only MPH showed WM load-dependent effects in the left IFC. Left IFC is involved in subvocal rehearsal processes during WM tasks (Owen et al., 2005; Smith et al., 1998). Thus, the left IFC was upregulated within patients and enhanced in patients relative to controls only by MPH.

In addition, during the TD and the SST tasks, MPH showed also some left-lateralised effects that were stronger than those of ATX. However, it is important to note that in these tasks the effects of MPH were not restricted to the left hemisphere. Thus, during TD, only MPH completely normalised the underactivation observed in children with ADHD under placebo compared to healthy control boys in left IFC and putamen.

Finally, activation in the left basal ganglia and premotor cortex (reaching into left IFC) was enhanced in ADHD boys relative to healthy controls during motor execution processes only after a single dose of MPH. These left lateralised findings are in line with previous studies where the effect of MPH administration in children with ADHD was most prominently left-lateralised (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Christakou, et al., 2009), as well as with

some evidence for a left-lateralised bias in the dopaminergic system (Flor-Henry, 1986; Glick et al., 1982). Therefore, the findings are suggestive of a potentially stronger effect of MPH on most prominently left-lateralised networks including the basal ganglia, left IFC and premotor regions and ACC/SMA. However, it cannot be overlooked that the effects of MPH were not exclusively left lateralised, and therefore further studies are needed in order to clarify the potential laterality effects of MPH. Alternatively, these results may have been due to the combined effect of MPH on both DA and NE.

This is particularly interesting in contrast with the drug-specific effects of ATX, which were more predominantly (although not exclusively) right lateralised. During the WM task, and compared to MPH, ATX showed drug-specific right-lateralised upregulation effects within patients in the right DLPFC, a key region for the manipulation and storage of information during WM processes (Owen et al., 2005). The reduced activation in this region shown by ADHD boys under placebo relative to controls was also normalised under ATX. In addition, both compounds enhanced activation in children with ADHD relative to controls in fronto-STG-striatal regions during WM. However, only when ADHD boys were under ATX did it reach the right IFC, which has been shown to be involved in WM load processing (Baier et al., 2010). Therefore, these findings suggest that the effects of ATX may be stronger on right lateralised prefrontal regions, in line with the evidence for more strongly right-lateralised fronto-parietal noradrenergic networks, which underlie arousal, phasic alertness and attention processes (Tucker & Williamson, 1984). Furthermore, as described in Chapter 3, phasic responses of the noradrenergic system have been shown to act as an attention filter that selectively modulates the responsiveness of task-related cortical circuits (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003). This would be in line with previous evidence from non-human primates, where ATX showed potentially stronger effects on noradrenergic than on dopaminergic systems during WM (Gamo et al., 2010).

Thus, while ATX showed drug-specific effects that were right-lateralised, potentially reflecting its effects on right-lateralised noradrenergic networks involving prefrontal regions (Tucker & Williamson, 1984), MPH showed some left-lateralised effects, which may reflect the left-lateralised bias of the dopaminergic system (Flor-Henry, 1986; Glick et al., 1982). It is important to highlight at this point that in prefrontal regions, DA is reuptaken by the NET given the reduced presence of DAT

in these regions (Moron et al., 2002; Yamamoto & Novotney, 1998). Therefore, as ATX is a selective presynaptic NET blocker (Bymaster et al., 2002) and MPH has been shown to block both DAT and NET (Hannestad et al., 2010; Volkow, Wang, Fowler, Gatley, et al., 1998), both drugs enhance DA and NE in prefrontal regions (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006). Consequently, both drugs may have acted on both DA and NE systems, although the results are suggestive of slightly differential stronger effects of the two drugs on one neurotransmitter system over the other, given the stronger left lateralisation of the dopaminergic system (Flor-Henry, 1986; Glick et al., 1982) and the stronger right lateralisation of noradrenergic systems (Tucker & Williamson, 1984).

9.4. Shared effects

The results show a significant degree of overlap of the effects of MPH and ATX on performance and brain activation during the different paradigms.

During the WM task, both drugs showed shared effects on performance and brain activation. Both MPH and ATX normalised the increased number of errors made by patients under placebo relative to controls in the more difficult conditions of the task. Furthermore, both drugs showed enhanced fronto-STG-striatal activation. There is evidence for the involvement of cortico-striato-thalamic-cortical neural networks in the maintenance of information in WM (Frank, Loughry, & O'Reilly, 2001; Jonides et al., 1997; Wang, 2001). Thus, both drugs may have upregulated this network and improved WM function, which is supported by the association between the enhanced activation in this network and performance under both drugs. It would be interesting to study the effects of more selective compounds that affect only one of these two neurotransmitters, as that would allow to elucidate the relative role of the different neurotransmitters in the enhanced activation observed in this network. The effects of MPH on striatal activation are not surprising, as these were hypothesised based on previous evidence of basal ganglia blockade of DAT effects of MPH (Bymaster et al., 2002; Volkow, Wang, Fowler, Gatley, et al., 1998), as well as on normalisation effects of MPH during WM tasks in this region (Pohn-Kristensen et al., 2011). However, the enhanced striatal activation when patients were under ATX was unexpected. At present, and as mentioned in the previous section, we hypothesise that these striatal effects may be due to direct noradrenergic effects of ATX on frontal and

thalamic activation, which may indirectly have enhanced striatal activation within fronto-striato-thalamic networks (Easton et al., 2007; Nijima et al., 2010).

In addition, during the WM task there were shared WM load-dependent enhanced deactivation effects, which we hypothesise were due to enhanced deactivation of the DMN. However, these differed in their location and timing: when under MPH, these effects were observed only during the 2-Back condition and were located in bilateral occipital regions and precuneus, whereas the deactivation effects of ATX were stronger with increased WM-load and localised in midline ACC-PCC regions. Although only MPH has been previously shown to enhance the deactivation in the DMN during different cognitive tasks in children with ADHD (Liddle et al., 2010; Peterson et al., 2009), both drugs significantly deactivated the DMN in healthy adults during WM (Marquand et al., 2011). However, Marquand et al (Marquand et al., 2011) also showed that compared to each other, MPH had greater enhancing effects on WM networks, while ATX had stronger deactivation effects on the DMN. Although the DMN has more frequently been associated with dopaminergic regulation (Delaveau et al., 2010; Tomasi et al., 2009), it has also shown to be sensitive to noradrenergic manipulations (Minzenberg, Yoon, & Carter, 2011). The reduced presence of DAT in occipital cortices (Ciliax et al., 1999) and the presence of NET in cingulate regions (Smith, Beveridge, et al., 2006) suggest that the involvement of NE in the regulation of the DMN may be highly relevant. However, and as mentioned in previous sections of this chapter, it is possible that both drugs had an effect on both neurotransmitters systems not only in PFC (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006) but also in other cortical brain regions, which could also explain some of the observed shared effects in fronto-temporo-striatal regions.

Therefore, the results highlight the need for studies on the compared effects of both drugs in ADHD patients on the DMN across different cognitive tasks to further confirm or refute this finding. As suggested above, the use of compounds with more selective effects on these two neurotransmitters would help to elucidate the relative role of each neurotransmitter on the DMN in ADHD patients.

However, alternative explanations for the deactivation observed in the occipital regions and precuneus when patients were under MPH relative to healthy controls are also plausible. The lack of association between movement parameters and brain activation within patients suggests that the clusters of activation differences

between groups are unlikely to be due to movement artefacts in the patient group. However, this should be further tested with larger sample sizes to be totally excluded. Alternatively, MPH may have affected the dopamine/acetylcholine imbalance, necessary for adequate cognitive functioning (Levin et al., 1990), by increasing DA-regulated IFC activation during the 2-back condition, and by downregulating cholinergic function in occipital regions, which would suggest reduced bottom-up visual-spatial processing. However, given the association between the reduced brain activation in these areas and improved performance in the task, the previous evidence of reduced activation in such regions in children with ADHD (Booth et al., 2005; Hart, Radua, Nakao, et al., 2012; Rubia, Halari, Cubillo, et al., 2011; Rubia, Halari, Mohammad, et al., 2011; Vance et al., 2007) and its normalisation after MPH administration (Rubia, Halari, Mohammad, et al., 2011), it seems unlikely that this may be the case, although future studies should further investigate more closely the effects of MPH on occipital, cuneus and PCC regions.

During the SST, both drugs showed shared normalisation effects in left VLPFC, which was underactivated in patients under placebo relative to controls. Activation in this region may be associated with improved inhibitory function, given the evidence for its role during motor response inhibition processes (Nee et al., 2007; Swick et al., 2008). However, given previous evidence of the involvement of this region on performance monitoring processes (Derrfuss et al., 2005) and its upregulation/normalisation after a single dose of MPH in children with ADHD (Rubia, Halari, Mohammad, et al., 2011), we hypothesised that these effects would be due to improved performance monitoring processes. The shared effects of both drugs may be due to the upregulation of the dopaminergic and/or noradrenergic systems, as both drugs enhance extracellular levels of DA and NE in prefrontal regions (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006).

However, our findings suggest that, at a dose of 1mg/kg, ATX may have stronger effects on performance monitoring rather than on motor response inhibition neural networks. This would be in line with the hypothesised role of the noradrenergic system as an attention filter that upregulates higher task-related cognitive processes necessary for the detection of the relevant/salient stimuli (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003). However, as described in the previous section, the potential effects of the dose of ATX administered needs to be taken into account.

Hence, studies on the effects of different doses of ATX and MPH are needed to confirm this aspect.

During TD, both drugs showed shared moderate normalisation effects in right IFC, which was underactive under placebo relative to controls. Time perception processes have been shown to be sensitive to dopaminergic manipulations, in line with the suggestion of its dopaminergic innervation (Baldwin et al., 2004; Ben-Pazi et al., 2006; Rammsayer, 1999; Rubia, 2006; Rubia, Halari, Christakou, et al., 2009; Rubia, Noorloos, et al., 2003; Smith et al., 2003). Thus, the shared but only moderate normalisation effects of both drugs are likely to be associated with the potential upregulation of the dopaminergic system in prefrontal regions.

Alternatively, ATX may have enhanced a right-lateralised noradrenergic attention network, which may have modulated the responsiveness of task-related TD dopaminergic frontal cortical circuits (Berridge & Waterhouse, 2003; Aston-Jones & Cohen, 2005).

On the other hand, MPH showed shared effects on right IFC, drug-specific performance improvement within patients, stronger effects on left IFC and drug-specific effects on SMA/ACC activation, which are key regions for TD processes (Koch et al., 2009; Rubia, 2006; Rubia & Smith, 2004; Shih et al., 2009; Wiener et al., 2010). Taken together, the results suggest that MPH modulated activation on all the different components of the TD neural network, which may have thus improved performance during the task.

These findings highlight several aspects that merit further investigation. One open question is whether moderate effects on different key regions for the cognitive function studied would be enough to improve such function. The evidence from the present study suggests this may be the case; however, studies on the compared effects of different doses of MPH and ATX may help clarify this point. This finding highlights the need for further additional research on the compared neurofunctional effects of both drugs during TD processes, whether these effects are dose-dependent and how they are compared over time after prolonged administration.

9.5. Conclusions

In conclusion, single dose challenges of MPH and ATX in medication-naïve children with ADHD showed shared and drug-specific effects, which were highly task-dependent, and are suggestive of potential differences in the beneficial effects of

the drugs. There was a significant degree of overlap between the effects of both drugs, with shared effects observed across tasks in cortical networks including bilateral IFC, fronto-temporo-striatal regions and DMN. Nevertheless, while MPH significantly improved performance and brain activation during TD, motor execution and motor inhibition processes, ATX differentially enhanced brain activation in key regions for WM processes. These task-dependent and drug-specific effects suggest potential differential effects of the two drugs on different cognitive processes. These effects can be confirmed after long-term drug administration, which could potentially lead to individually tailored treatments based on which areas are most impaired in each patient.

The most relevant findings, which are task-dependent effects of the drugs, can furthermore be interpreted in light of previous theoretical approaches of ADHD. As reviewed in Chapter 1, ADHD has been described as a disorder whose symptoms may arise from deficits in behavioural inhibition processes due to dysfunctional fronto-striatal regions (Barkley, 1997); deficits in WM resulting from a dysfunctional dorsolateral prefrontal cortex (DLPFC) (Castellanos & Tannock, 2002), or deficits in reinforcement processes as a result of underfunctioning nigrostriatal dopaminergic systems (Sagvolden et al., 2005).

However, the results from the present study would potentially be better related to other approaches. Thus, ADHD has been described as a disorder affecting multiple neural systems, with structural and functional abnormalities in functional networks underlying the cognitive deficits observed (Hart, Radua, Mataix-Cols, et al., 2012; Hart, Radua, Nakao, et al., 2012; Makris et al., 2009; Nigg & Casey, 2005). Thus, the results of the present study suggest that despite a significant overlap on the effects of both MPH and ATX on brain activation, they also have task-specific effects on the functional networks underlying the cognitive functions studied. Should single dose and long-term studies in larger samples confirm this aspect, this would help to the design of better treatment plans, individually tailored, given the evidence that shows how different subtypes of children with ADHD may have deficits in one cognitive domain and not others, i.e. they may present with deficits in temporal processing but not inhibitory functions (Nigg et al., 2005; Sonuga-Barke et al., 2010), and the fact that depending on the functional abnormalities underlying the cognitive deficits the patient presents with, one of the medications may be better suited for the treatment of a particular subject.

Alternatively, Sergeant (Sergeant, 2000) proposed that ADHD symptoms would arise from an arousal/activation dysregulation, in which arousal deficits would be due to a hypofunctioning right lateralized noradrenergic neural system, and activation deficits would arise from a hypofunctional dopaminergic network. Both MPH and ATX are effective medications for the treatment of ADHD, with neurofunctional effects in the neural systems hypothesised by Sergeant as core to the disorder. Indeed, as it has been shown, ATX showed effects that were stronger (but not limited to) right-lateralised prefrontal regions, potentially due to its stronger (although not exclusive) effects on noradrenergic systems, whereas MPH showed stronger effects on (albeit not limited to) dopaminergic fronto-striatal networks. Hence, the present study suggest that although both drugs affect DA and NE in prefrontal regions, the two compounds may be differentially suited to treat the deficits shown by children with ADHD, with ATX being better suited to improve arousal deficits and MPH better suited for activation dysregulation. More studies would be needed to further clarify this aspect.

9.6. Strengths and limitations of the study

The main strength of this study is the double blind, randomised, placebo-controlled, cross-over design, together with the recruitment of a sample of boys with ADHD who had never been on stimulant medication before. As discussed in the introductory chapters of this thesis, this avoids the most important confound of a pharmacological study in ADHD, which is the previous history of stimulant medication, shown to have long-term effects on brain structure and function (Frodin & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011). Furthermore, this study recruited a relatively large sample for an fMRI study, whose homogeneity was ensured by the recruitment of only boys, with the combined subtype of the disorder, and with only 2 of the participants with a confirmed diagnoses of CD/ODD.

The present study furthermore provides evidence of the usefulness of a relatively unusual approach. Pharmacological studies can be typically classified in two types. The present study would be placed in between the two types, filling the existing gap between them. This has its strengths and limitations.

Both animal and human PET studies on the mechanisms of action of the drugs allow for the identification of the specific neurotransmitter or transporter location where in the brain the drugs are acting, either after a single dose or how the long-term

administration of such drug may modify the expression of determined neurotransmitter or its function. However, it needs to be considered that these studies typically focus on single neurotransmitter systems, making it therefore difficult to extrapolate the results from such studies from neurochemical effects to behaviour, as the different neurotransmitter systems do not act in isolation but intensely interact between them.

Clinical pharmacological fMRI studies allow on the other hand for the identification of the neurofunctional effects of the drugs and their association with the behavioural changes observed (e.g, symptoms and/or cognitive functions). Pharmacological fMRI studies can focus on the effects of a single dose of a drug, or on the long-term effects of the administration of the drug. Most often, single doses studies are conducted in healthy subjects, whereas on clinical populations typically the main interest is on the effect of long-term administration of such drug. However, it is important to note that the effects of single doses of the drugs must also be studied in clinical populations, as their effects may differ between clinical and healthy populations.

Furthermore, there are a number of factors to consider when interpreting the results of the long-term effects of a given medication on brain activation and cognitive function. First of all, the potential symptomatic improvement experienced by patients after long-term medication administration may have an impact on brain function and cognition. It is therefore difficult to disentangle which of the observed effects are due to the drug administration and which are due to the symptomatic improvement. The presence of potential side effects such as dizziness, nausea or sleepiness may also affect brain function and cognition and therefore constitute potential additional confounding factors. Furthermore, and most importantly, long-term administration of a drug may lead to changes in brain structure and function, such as those described for MPH (Frodol & Skokauskas, 2012; Konrad et al., 2007; Nakao et al., 2011; Shaw, Sharp, et al., 2009). Therefore, such studies cannot unequivocally conclude on the potential effects of these drugs on the cognitive functions studied and the underlying brain activation, as those confounding factors are inherent to the long-term administration of the drug.

Therefore, studies on the effects of the administration of single doses of a drug allow for the identification of the effects of a drug avoiding such confounding factors. Such studies also allow to refine the design of studies of long-term effects, based on

the data of the effects of single doses of the drug. Since these studies do not suffer from the potential effects of symptomatic improvement, their results can be more directly associated with the drug administration, and allow for better hypotheses on the potential long-term effects of the drug on brain function and cognition. Thus, studies like the present one constitute the intermediate step necessary to achieve a comprehensive understanding of the effects of drug administration on brain activation, cognitive functions and the way they modify symptoms and behaviours.

The use of a single dose of MPH and ATX was chosen to avoid those potential confounds associated with long-term administration. Thus, the study allows for the identification of the compared effects of both drugs on brain activation during cognitive functions typically impaired in patients with ADHD and which are potential target of the treatment. This study thus helps to identify the effects of each drug on brain activation and cognition *before* any clinical effects are manifested, and therefore it is less likely to be confounded by symptomatic improvement. Based on this, the potential differential effects the drugs will have on brain function during different cognitive processes can be more precisely hypothesised, thus guiding the design of studies on the compared effects of long-term administration. As an example, it could be hypothesised that ATX will have stronger or at least faster effects on working memory function, as it showed more pronounced effects than MPH after a single dose. Furthermore, and given the preliminary knowledge from animal, single cell and human PET studies, these studies also enable us to hypothesise on the potential neurotransmitters involved in the different cognitive functions, which may potentially underlie the symptomatic presentation of the disorder.

Therefore, this study makes a relevant contribution towards a preliminary understanding of drug-specific effects on brain activation and cognition.

However, the results from the present study have to be interpreted in light of its limitations. These have already been mentioned in Chapters 6-8, during the individual discussions of each of the chapters, but will be discussed more in depth here.

This study recruited right-handed ADHD boys with the comorbid subtype of the disorder, which limits the generalizability of the findings.

Healthy control boys were scanned only once and unmedicated, while children with ADHD were scanned on three occasions, which may have led to the presence of potential practise effects. The results suggest there were no such practise effects

within patients. However, this does not control for the differential practise effects when comparing their performance and brain activation in children with ADHD to that of healthy control boys. Furthermore, the assumption of the lack of practise effects within patients needs to be considered with caution, as the sample size is too small to adequately test this. The reduced number of subjects on each condition of the randomisation order does not allow to test for potential sequence effects, which should be tested in further studies with larger sample sizes.

The difference in IQ between groups is an additional limitation. It has consistently been reported that ADHD patients show lower IQ compared to healthy control subjects (Bridgett & Walker, 2006; Dennis et al., 2009). Low IQ is part of the disorder, and therefore it is not possible to control for IQ differences between groups without removing part of the variance associated to ADHD (Evans & Anastasio, 1968; Miller & Chapman, 2001).

This is particularly problematic in the case of WM. WM has been shown to be closely associated with IQ, with additional indirect evidence suggesting that IQ and WM may share a common neurofunctional base, with the DLPFC being a key region for both functions (Conway et al., 2003). WM is indeed one of the measures obtained in widely used tests of general intelligence such as the Wechsler Intelligence Scale for Children (4th version) (WISC-IV) (Wechsler, 2004). Therefore, in the WM task, we did not covary for IQ but repeated the analyses after excluding outliers, and the findings remained although at a slightly more lenient p-value. Another possibility commonly used is to covariate for IQ differences between groups (ANCOVA analysis). IQ has been shown to be a moderator of the differences between ADHD patients and healthy subjects during motor inhibition (Lipszyc & Schachar, 2010; Willcutt et al., 2005) and TD tasks (Paule et al., 1999; Wearden et al., 1997). In these tasks, we conducted preliminary case-control WB analyses with and without using IQ as a covariate, in order to help to determine the impact of IQ on the differences in brain activation between healthy controls and children with ADHD under placebo. During TD, covarying for IQ restricted the areas of between group differences in brain activation to those typically described as most closely associated with TD networks, including the IFC and SMA/ACC (see Chapter 8). On the other hand, during the SST, the areas of brain activation differences between groups were the same as when IQ was not used as a covariate, but at a higher p value (see Chapter 6). Hence, we conducted the rest of the analyses in the TD using IQ as a covariate, and

without IQ as a covariate in the case of the SST. Thus, the results suggest that the presence of IQ differences between the groups moderated but did not explain the differences on brain activation between groups or the effects of both compounds on brain activation.

The healthy control group showed a wider age range relative to the ADHD boys, despite no differences in mean age. Taking into account that patients with ADHD show a neurodevelopmental delay (Rubia, 2007; Shaw et al., 2007; Shaw et al., 2012), future studies should ideally more closely match the age ranges of both groups.

Another potential limitation is the presence of drop-outs in the sample. We recruited 30 patients with ADHD. Of these, 4 (13%) (2 participants under placebo, 2 under ATX) terminated their participation in the study prematurely, due to their inability to tolerate the scanning situation, which is commonly reported in fMRI studies of children. One subject (3%) was excluded due to his low IQ, another one due to the presence of neurological abnormalities and a third one due to braces. Data from another 2 subjects (7%) were not usable or lost due to technical problems. During the Stop task, one additional subject had to be excluded due to technical problems during the task (incorrect positioning inside the scan, too tilted) and another one due to incorrect performance of the task (with >60% omission errors). During the WM task, one subject had to be excluded due to excessive movement inside the scan (>3mm). The need to recruit subjects who show minimal motion parameters while inside the scan needs to be considered: it may be that only those subjects with less pronounced hyperactivity symptoms have been recruited. However, the differences in SDQ and Conners' scores (where the specific DSM-IV hyperactivity subscale showed values of $T > 80$ in the ADHD group) suggest that the group of children with ADHD showed severe hyperactivity symptoms.

The study was designed to compare effects of single doses of MPH and ATX administration on brain activation and performance in medication-naïve children with ADHD, and constitutes the first step towards an understanding of their differential mechanisms of action. However, it needs to be taken into consideration that MPH and ATX have very different time courses to reach their maximum clinical efficacy. While behavioural effects are typically reported after a single dose of MPH (Greenhill et al., 2001), ATX requires 10-12 weeks to reach maximal efficacy for symptomatic improvement (Hazell et al., 2010; Montoya et al., 2009). Thus, the design of this

study may initially seem unfavourable for ATX, as less pronounced effects would be expected. However, when children with ADHD were under ATX, drug-specific upregulation effects within patients and normalisation effects relative to MPH were observed in the key WM region of right DLPFC. Furthermore, ATX showed significant effects in left VLPFC activation during the SST, and moderate effects on activation in right VLPFC and cerebellar regions during the SST, and in right IFC during the TD task. This is highly relevant, as it suggests that ATX may show beneficial effects on cognition and brain activation before behavioural effects are evident. Different dosages and/or prolonged treatment may have resulted in stronger effects. Thus, whether these effects are dose-dependent and how stable they are in time can only be studied in follow-up longitudinal studies.

The main goal of the present study was the investigation of the compared effects of both drugs on brain activation. Despite the presence of drug-effects on performance measures, this study may have been underpowered to identify neuropsychological performance differences in the different cognitive tasks used.

Because of the design of the study, focused on the compared effects of a single dose challenge of MPH and ATX, the results cannot be extrapolated to clinical settings at present. However, this leads to the next question, open for future studies: what are the compared effects of MPH and ATX on cognition and brain function in ADHD after their prolonged administration?

9.7. Future directions

MPH and ATX are routinely prescribed to treat ADHD. However, their mechanisms of action on brain function in ADHD are relatively unknown. Studies on MPH have shown it has upregulation and normalisation effects in children with ADHD in prefrontal and striatal brain activation during motor inhibition tasks (Epstein et al., 2007; Rubia, Halari, Mohammad, et al., 2011; Vaidya et al., 1998), in bilateral prefrontal regions, ACC and cerebellum activation during TD (Rubia, Halari, Christakou, et al., 2009) and in prefrontal and striatal activation during WM (Prehn-Kristensen et al., 2011; Sheridan et al., 2010). However, nothing was known on the drug-specific brain function effects of MPH relative to ATX and nothing was known on effects of ATX in ADHD brain function. Therefore, the present study constitutes a pioneering step towards a first understanding of their compared effects on brain function in ADHD.

The focus of the study on a single dose challenge of MPH and ATX precludes the findings from being extrapolated to clinical settings at present. Future studies should ideally include a battery of tasks comprising both executive and non-executive functions so as to identify whether the effects of the drugs are task-specific, limited to executive functions or also affect other non-executive cognitive functions. Furthermore, this would shed some light on which aspects of cognition respond better to which medication, and how this is associated with changes in brain activation. As mentioned in the previous section, this study can be considered as the first step to understand the neurofunctional effects of both medications on brain activation of children with ADHD, and their potential selective benefits. Following the results of the present study, studies on longer-term effects of both drugs or longitudinal follow-up tests with different timepoints would help to identify the different time courses of the effects of both drugs across different cognitive domains. Furthermore, such studies would also clarify whether the time courses of the drugs on cognition and brain activation parallel those described for symptomatic improvement.

Clinicians commonly report the need for a progressive increase in the doses of stimulants used in order to maintain the beneficial effects of the drugs on symptoms of ADHD. It has also been reported that the superior beneficial effects of medication therapy compared to other therapies fade after 3 years of treatment (Jensen et al., 2007). Longitudinal studies on the effects of MPH and ATX would allow one to identify the stability of those drug-related cognitive and brain activation changes over time. To achieve this, several key time points would need to be identified: 1) measures at baseline, 2) measures at the time when both drugs have reached their maximum clinical efficacy, and 3) measures after long-term treatment, as this has shown to have effects on the dopaminergic system (Fusar-Poli et al., 2012), brain structure (Frodl & Skokauskas, 2012; Nakao et al., 2011) and brain function (Konrad et al., 2007).

Another aspect that merits further investigation is the effect of different doses on cognitive function and brain activation. Some neuropsychological studies on the effects of MPH have addressed this issue (Bedard et al., 2002; Bedard & Tannock, 2008; Coghill et al., 2007; Gunther et al., 2010; Konrad et al., 2004; Lijffijt et al., 2006; McInnes et al., 2007; Scheres et al., 2003; Shiels et al., 2009; Spencer et al., 2009; Tannock et al., 1989; Tannock, Schachar, et al., 1995), with results suggesting that dose-effects may be task-dependent. Thus, linear effects with more pronounced

improvements at higher doses have been reported during change-RT (Tannock, Schachar, et al., 1995) and attention tasks (Gunther et al., 2010; Konrad et al., 2004). Meanwhile, an inverted-U relationship between dose and performance has been reported during focused attention or sustained attention tasks (Gunther et al., 2010). However, results are more controversial with regards to motor inhibition tasks (Coghill et al., 2007; Konrad et al., 2004; Lijffijt et al., 2006), and during auditory-verbal WM tasks (Bedard & Tannock, 2008; McInnes et al., 2007; Tannock, Ickowicz, et al., 1995), where the linearity of the behavioural effects has not been clearly established. Furthermore, no study has focused on dose-dependent effects of ATX on cognition, and there are no fMRI studies on the compared effects of different doses of MPH and ATX on brain activation in ADHD patients. Given the inverted-U mode of function of both dopaminergic and noradrenergic systems, which furthermore varies depending on the different cognitive functions, it seems necessary to assess the effects of different doses of both compounds on a battery of cognitive tasks in ADHD patients.

Finally, another area where more research is needed is on the presence of abnormalities in the noradrenergic system of patients with ADHD. PET studies in adults with ADHD (as PET cannot be used in children), would help to identify the presence of abnormalities in the NE system in ADHD. However, advances in this area depend greatly on the development of adequate radioligands for the NET and NE receptors. Nevertheless, once these radioligands are available, PET studies should help to clarify not only those abnormalities but also the compared effects of both drugs on the noradrenergic system, both after single doses and after prolonged administration. Furthermore, such studies may help to elucidate whether the clinical response to ATX and/or MPH may be associated with the presence of abnormalities in NE systems, which is unexplored thus far. The evidence from this field, together with that from fMRI studies in ADHD patients on the compared effects of both drugs on brain activation and performance during cognitive tasks, would significantly increase our understanding of the compared mechanisms of action of both drugs in ADHD.

9.8. Final remarks and conclusions

This PhD has provided the first evidence of the compared effects of single doses of MPH and ATX on brain activation during task-relevant cognitive tasks in ADHD patients.

The main conclusions of the study can be summarised as follows:

a) The effects of both drugs on performance and brain activation are highly task-dependent. Drug-specific effects were observed for MPH during TD and motor execution processes, whereas the drug-specific effects of ATX on brain activation were restricted to WM. Furthermore, both drugs showed normalisation effects during the motor response inhibition task, although these were only moderate for ATX but significantly stronger for MPH on right VLPFC-cerebellar regions. These results could have implications for treatment indications. However, these drugs are not administered on a single dose basis but over prolonged periods of time. Therefore, these results can be considered as the first step to the understanding of the drug-specific and shared effects of both drugs on brain function in ADHD patients and should be considered in the design of studies on the compared effect of prolonged administration of both drugs on cognitive function and brain activation, which would be the following step to further achieve a better understanding of the mechanisms of action of both drugs.

b) The drug-specific effects of MPH and ATX showed a differential pattern of lateralisation in prefrontal regions, which were more prominently left-lateralised for MPH and right-lateralised for ATX, in line with evidence for a hemispheric bias in dopaminergic and noradrenergic systems (Flor-Henry, 1986; Glick et al., 1982; Tucker & Williamson, 1984). These results suggest that despite the shared effects on DA and NE on prefrontal regions (Berridge et al., 2006; Bymaster et al., 2002; Swanson et al., 2006), MPH may have a more prominent effect on left-lateralised dopaminergic networks, while ATX may have a more prominent effect on right-lateralised noradrenergic networks. However, whether this lateralisation effect is task-dependent, or really present needs to be further studied.

c) There is a significant overlap between the effects of both compounds on brain activation, which goes beyond the expected overlap in PFC, such as shared normalised in left VLPFC activation during motor inhibition, in right VLPFC during TD, shared enhanced fronto-temporo-striatal activation reaching into the thalamus and shared deactivation of the DMN. A significant proportion of children with ADHD

have been shown to respond positively to both medications (Sangal et al., 2006). Therefore, future longitudinal studies focused on the compared effects of both drugs on cognition, brain activation and symptoms should investigate whether these shared effects on brain function underlie the positive effects of both medications on clinical symptoms in that subgroup of children with ADHD that respond positively to both medications.

d) The effects of ATX on cognition and brain activation were observed after a single dose. This is highly interesting, as it suggests that these effects may be observed before the behavioural effects, which typically take a minimum of 4-6 weeks of persistent treatment (Montoya et al., 2009). However, whether the effects of ATX are observable on cognition and brain activation before significant symptomatic improvement is observed, and how stable these effects are in time can only be studied using longitudinal studies. Future longitudinal studies should further investigate whether these effects become stronger at different doses or with prolonged administration.

This investigation on the effects of MPH and ATX in medication-naïve patients is a first step towards improving our understanding of their drug-specific effects on brain activation and cognition, avoiding potential confounds of long-term treatment such as symptomatic improvement, side effects or chronic effects on brain activation.

The study makes a novel contribution to the field, as it compares for the first time the effects of both drugs on brain function in ADHD, and shows that both MPH and ATX have shared and task-specific effects on brain activation even after a single dose. Relative to ATX, MPH showed stronger effects on brain areas that are crucial for TD, motor execution and motor response inhibition processes, while ATX showed stronger effects than MPH on brain regions that mediate working memory. Given the differences of the two drugs in their temporal courses to clinical efficacy, however, further studies on the compared effects of prolonged administration of both drugs on cognitive deficits and the activation of the underlying neural networks seem necessary in order to extrapolate these findings to clinical settings.

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APPENDICES

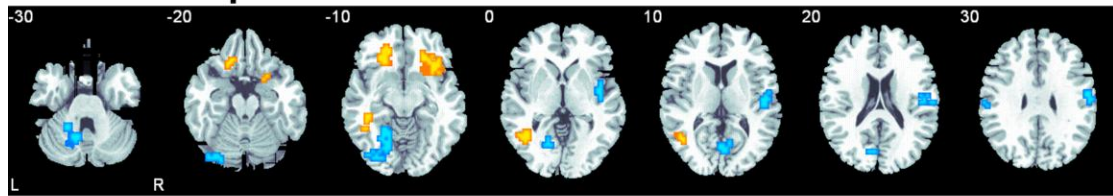
- Appendix Figure A1: Results of the between-group ANCOVA comparisons between healthy control boys and ADHD under either Placebo, Methylphenidate or Atomoxetine for the successful inhibition-Go trials contrast using IQ as a covariate.

- Appendix Figure A2. REsults of the between-group ANCOVA comparisons between healthy boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine after exclusion of outliers subjects with regards to IQ.

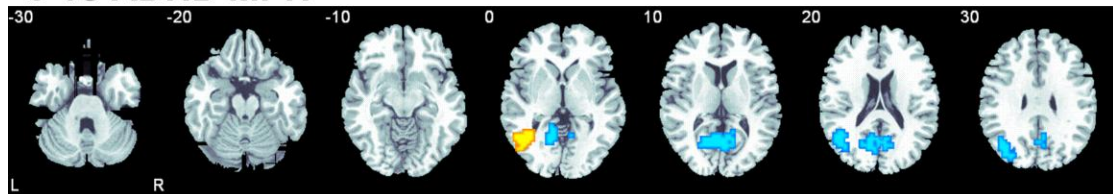
- Appendix Figure A3: Results of the between-group ANOVA comparisons between healthy control boys and ADHD under either Placebo, Methylphenidate or Atomoxetine for the Time Discrimination- Temporal Order Judgement contrast without IQ as a covariate.

Successful inhibition – Go trials

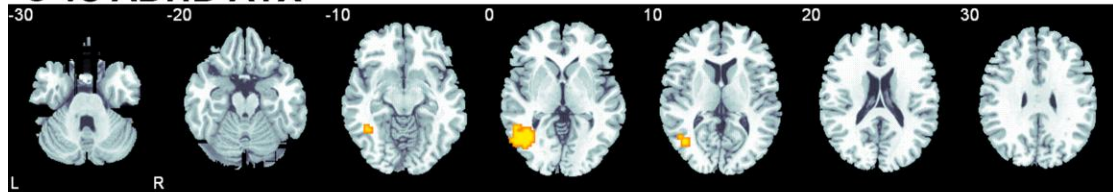
C vs ADHD placebo



C vs ADHD MPH

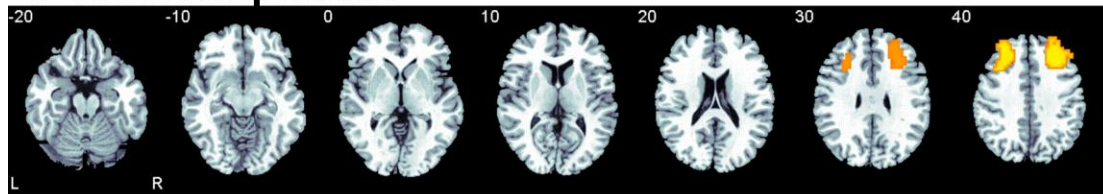


C vs ADHD ATX

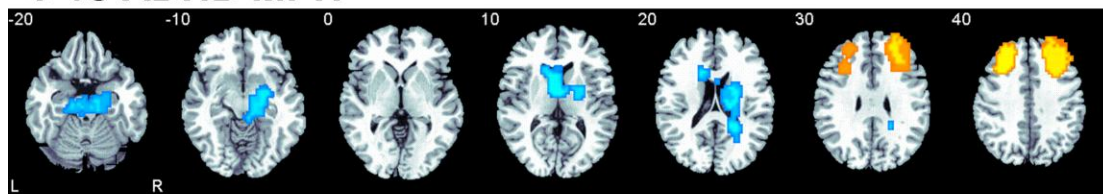


Appendix Figure A1. Between-group ANCOVA comparisons between healthy control boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine for the successful inhibition-Go trials contrast with IQ as a covariate. Axial sections showing the ANCOVA between-group differences in brain activation between healthy control boys and boys with ADHD under each drug condition (Placebo, MPH, ATX) during successful inhibition in the Stop task. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

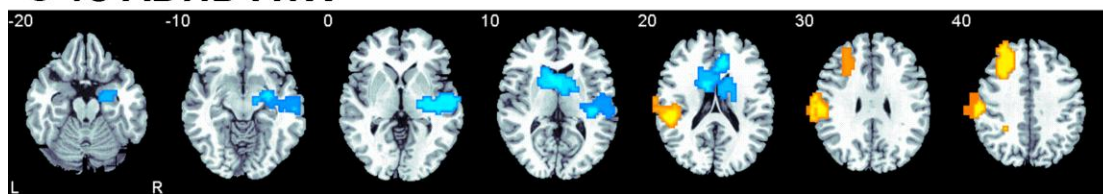
C vs ADHD placebo



C vs ADHD MPH



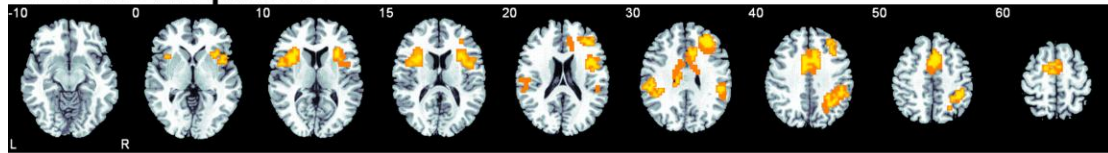
C vs ADHD ATX



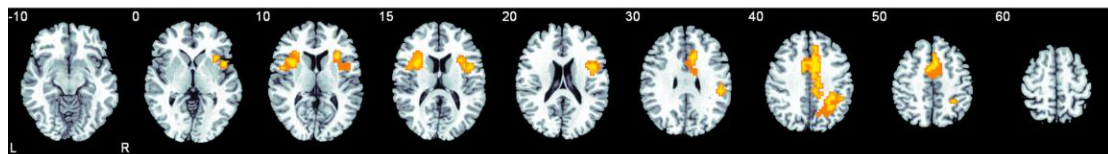
Appendix Figure A2. Between-group ANCOVA comparisons between healthy boys and boys with ADHD under either Placebo, Methylphenidate or Atomoxetine after exclusion of outliers subjects with regards to IQ. Axial sections showing the ANCOVA between-group difference effects in brain activation between healthy control boys and boys with ADHD under each condition (placebo, MPH, ATX). Clusters in orange denote areas where control boys showed enhanced activation compared to ADHD boys, clusters in blue denote areas where ADHD boys showed enhanced activation compared to control boys. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain

Between-groups ANOVA comparisons

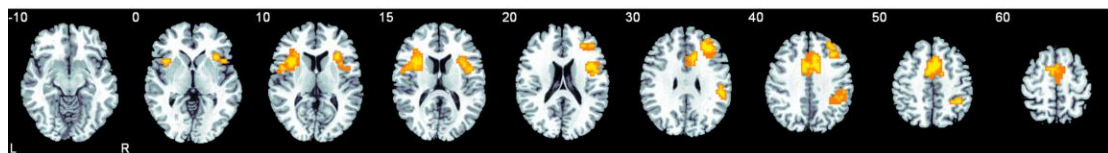
C vs ADHD placebo



C vs ADHD MPH



C vs ADHD ATX



Appendix Figure A3. Transversal images of the between-group ANOVA comparison between healthy control boys and boys with ADHD on a) placebo b) MPH c) ATX during time discrimination without IQ as a covariate. Slices are marked with the z-coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

In order to explore whether group differences in brain activation could be explained by significant group differences in IQ, we performed correlations between IQ scores and the SSQs of children with ADHD extracted from clusters of activation which differed between children with ADHD on placebo and controls. None of these were significant.